

Pedagogical Case Study

Vyndaqel (Tafamidis) Market entry in Portugal

Dissertation for obtaining the degree of Master in Business Administration

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Abstract

The main objective of this pedagogical case study is to analyse the market entry dynamics of pharmaceutical innovative drugs in Portugal, and the role and impact of the different stakeholders in this process. The case focuses on the market entry of Vyndaqel (Tafamidis) Pfizer's orphan innovative product to treat TTR-FAP, "*paramiloidose*", a highly incapacitating rare disease that has more than 2.000 diagnosed patients in Portugal, one of the highest prevalence worldwide and an incidence of 100 new patients every year.

In terms of methodology it were used two main sources of information. Regarding secondary data sources it was made an exhaustive search using the main specialty search engines regarding the Tafamidis case, market access, orphan drugs and market entry context in Portugal and Europe. In terms of primary data it were conducted 7 direct interviews with the main case stakeholders.

The pedagogical case study focuses on 5 main questions that provide the base of the discussion for the classes. First it is analysed the rationale behind the introduction of Tafamidis in Portugal, and its relevance for Pfizer, namely due to the previous investment made with the acquisition of FoldRX by \$400M, the company that developed the product in the first place. It is also analysed the point of view of the NHS, and the reasoning behind drug reimbursement that considered not only the technical (efficacy and safety) and financial benefits of the drug, but also the social impact, due to the major role played by patient associations' actions and coverage provided by the media that impacted the reimbursement decision. Finally it is analysed the vertical financing methodology that was selected by the Ministry of Health for drug acquisition by 2 public hospitals, that served as reference centres for the treatment of this disease.

Hugo Pedrosa wrote this case under the supervision of Professor Pedro Pita Barros as a dissertation to obtain the degree of Master in Business Administration, at the Lisbon MBA – UCP/Nova.

This case is based on real events.

1. Context

The year was 2012. The time of big blockbuster launches in the pharmaceutical industry was fading, with the reduction of the launch of new molecular entities (NMEs) in the market. R&D pipelines of major pharma companies were being pushed with the need to find new sources of revenue and future growth. One of the main strategies followed by big pharma companies was to enlarge their pipeline through the acquisition of well positioned biotech firms. These were very attractive, as they had the strategy of other start-ups, developing drugs within a fast entrepreneurial environment, where the risk is part of their daily lives, being able to do and redo their processes in a faster and agiler environment than large pharmaceutical companies do.

Most biotech firms tend to specialize in one or two main therapeutic areas in order to increase its focus and probability of success. This was the case of Fold Rx, an US based company created in 2003 that was bought by Pfizer in September of 2010¹. *"This transaction will add another important component to the growing portfolio of innovative in-line and investigational medicines for orphan and rare diseases within Pfizer's Specialty Care Business"* said Geno Germano, the president and general manager of Pfizer's Specialty Care Business Unit, *"and will complement the current and planned future research and clinical development taking place in Pfizer's Specialty Care Neuroscience disease area"*².

Fold Rx was specialized in neurodegenerative therapies, more specifically in the development of drugs for protein misfolding and amyloidosis related diseases. At the time of the acquisition the company was developing clinical studies with drugs to treat genetic neurologic and cardiovascular disorders. The most promising asset in its pipeline was the orphan drug Tafamidis (INN) that had recently completed a successful phase III clinical trial. This drug was a new hope for patients and families that suffered from Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP), a rare, neurodegenerative, genetically inherited disease, highly incapacitating in advanced stages. Like any other rare disease its prevalence was extremely low, roughly 1,1 per 100.000 people³. There were only 8.000 to 10.000 diagnosed patients worldwide⁴, with half of it in Europe. Nonetheless there was good potential in sales related to this innovative drug. The entry of this drug in the market would be a major breakthrough since there was no alternative treatment apart from liver transplantation. Transplantation consisted in removing the site

¹ <https://www.crunchbase.com/organization/foldrx-pharmaceuticals#sthash.QUCoSQhW.dpuf> – accessed 08/2015

² <http://www.fiercebiotech.com/story/pfizer-buys-foldrx-rare-disease-division/2010-09-01> – accessed 08/2015

³ INFARMED, "Tafamidis hospital use - Reimbursement report"; 2012

⁴ Benson MD, Kincaid JC. "The molecular biology and clinical features of amyloid neuropathy." *Muscle Nerve*. 2007;36:411-423

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where the amyloidogenic protein causing the dysfunction was synthesized, but it had high potential costs (both in health and financial terms) as the first year post transplant mortality rate was approximately 10%, affecting patients' willingness to use this path.

In November 2011 Pfizer was confirmed to have made the right acquisition. Vyndaqel, Pfizer's commercial name for Tafamidis received approval from the European Medicines Agency (EMA) showing positive statistically relevant results in terms of disease progression when compared to placebo. Even though there were no long term results a phase III clinical trial demonstrated that the proportion of patients with TTR-FAP who experienced no deterioration in neurological impairment (no progression of neurodegeneration) was higher in the Vyndaqel population. 60% against 38% in placebo population. Now it was crucial to get the product to the market and obtain NHS approval for its acquisition, because after the marketing authorization the product only benefits from the orphan drugs patent protection period during 10 years. After that period, generics may come to market with a similar treatment option. Now, more than ever, every launch was relevant, every market was to be approached properly in order to streamline the entry of the existing molecules, and Vyndaqel was no different.

This case focuses on analysing the entry of Vyndaqel (Tafamidis) in the Portuguese market.

Portugal was the primary market for this new drug as it had the highest prevalence of the disease worldwide. First patients ever to be diagnosed were from the northern region of Portugal, back in 1939. TTR-FAP patients already had a special regimen defined in the Law Decree 29/90, but nothing was stated related to patient's main concern in those days: how to obtain the product that claimed to be lifesaving. Pfizer had the same concern: how to get the product to the market so patients could benefit from it? Like any other innovative pharmaceutical drug its price had to pay the high investment in R&D so it was necessary to develop a strategy that involved and addressed the different needs and concerns of every stakeholder. Being Vyndaqel an orphan drug, intended to treat a rare disease, there was higher pressure on pricing since there were few patients to pay for it.

The context in 2012 was not favourable for product launches, as Portugal was under an economic intervention of TROIKA (composed by IMF, ECB, and EC) since the previous year. It had been implemented several budget cuts in healthcare with a high focus in the reduction of costs related to drugs. The reimbursement of an innovative drug would increase cost in the short term, but Pfizer had to prove the Ministry of Health that they had to do it.

2. Portuguese Healthcare System

Portuguese healthcare system is a mixed model between Beveridge and Bismarck, where the National Health Service (NHS), created in 1979 after the revolution, is the central piece of the system. The access to healthcare is one of the priorities of the Portuguese government, and in particular the Ministry of Health. A “Universal, general, and mainly free of charge NHS, taking into account the populations social and economic conditions”⁵.

The Ministry of Health (MoH) is financed centrally by the Government, via the Ministry of Finance. The MoH is in charge of planning and regulation of health in Portugal. The NHS is predominantly financed by general taxation⁶. About 2/3 of the health expenditure in Portugal is public, as in most developed countries⁷. The other third is mainly supported by the families (final payer), public and private health subsystems and voluntary health insurances (VHI) that is used by about 20%⁸ of the population, as a complement to the NHS. In this point it is relevant to state that Portugal is one the countries where the families contribute more to the financing of health directly, apart from what they already pay in their taxes and social security allowances that flow to the NHS⁹.

The evolution of the healthcare expenditure has always been a burning issue in all governments, even more in 2011, with Portugal applying the memorandum of understanding celebrated with Troika. Controlling expenditure, debt and overall reduce the government deficit, or at least bring it to satisfactory levels (<3% according to EU policies) were all relevant issues and a focus of the government.

Portuguese healthcare expenditure grew consistently from 2000 till 2010, with a growth rate higher than the growth of the GDP, except from 2006 and 2007, where the GDP grew more than the healthcare expenditure¹⁰. This showed a high level of investment and commitment towards the NHS itself, but also showed lack of control over expenditure. In 2010, the more than 17.600M€¹¹ spent on healthcare represented ~9,8% of the Portuguese GDP. This value pressured national accounts and was higher than those of countries similar to Portugal like Spain, Italy, Greece or Ireland (the latter two also interventioned by Troika). When analysing the origin of the costs, the majority of it is related to outpatient care (45%), which covers areas like outpatient or day-care hospital visits. Twenty three percent of the total is related to medical goods, mainly constituted by drugs (roughly 3/4) and medical devices (roughly 1/4)¹².

⁵ Constitutional Law nº1/2001 de 12 December – Art. 64º (Health)

⁶ Barros, P. “Health system in Transition, 2011

⁷ *Banco de Portugal* – “Portuguese pharmaceutical drug market analysis” - Vogler et al., 2011

⁸ *Associação Portuguesa de Seguradores*

⁹ OECD, Health at a glance 2013

¹⁰ OECD, Health at a glance 2013

¹¹ *INE, “National health account” 2012-2014P*

¹² OECD, Health at a glance 2013

3. Market access

For a drug to be introduced in the market there is a long, bureaucratic and costly process that is endured by pharmaceutical and biotech companies. The percentage of success is near zero if we consider that only one out of 10.000 molecules¹³ gets market authorization approval. Pharmaceutical products are patent protected in Europe for a period of 20 years after its registry that occurs when the molecule is “found”, what means that, on average, a product has 8-10 years of patent protection when it hits the market. The first 10-12 years of the patent period are spent on clinical research. The length in the time to hit the market is quite relevant as each year represents more costs and less sales to the pharmaceutical entity.

In 2010 the pharmaceutical industry invested, on average, about 15% of its net sales on R&D¹⁴, the leading sector on this ranking, as this industry relies heavily on new products. There is a continuous need to find the next blockbuster, which will reshape the market not only in terms of the people’s health, but also in terms of the companies’ “health”, meaning future growth and profitability. According to several studies, the cost of bringing one new molecular entity (NME) to the market rounds from 1.2 to 1.8 Thousand Millions USD¹⁵¹⁶. This cost is related to several factors. On the top is the high investment made on clinical trials before marketing approval, but there are also relevant costs on post approval phases. The low rate of products that hit the market is also relevant, has this failure cost must be incorporated in the costs of the successful products. Finally there is the opportunity cost of the investment that has to be taken into consideration in these analysis. As mentioned above the development time of a NME can take up to 12 years, meaning that there is a major gap between the investment made and its return¹⁷.

After getting market authorization for the commercialization of a product there is the need to prove its therapeutic added value against the best therapeutic alternative. These steps are crucial for the product’s success in the market, as the reimbursement of a product by the NHS depends on these components.

In countries like Portugal, where the NHS accounts for the major part of the National health expenditure and where the NHS serves as a “model” for the private market (that start applying the same conditions in their units), obtaining reimbursement and obtaining it fast is a major priority for pharmaceutical companies. The time to obtain reimbursement is quite relevant as it is burning time of sales. The later a product hits the market, the lower the probability of success. In Portugal, according to a study presented by APIFARMA the average duration for analysing a reimbursement request was 331 days, increasing to

¹³ EFPIA, “Pharmaceutical figures in numbers 2011”

¹⁴ EFPIA, “Annual review of 2011 and Outlook for 2012”

¹⁵ Deloitte, “Measuring the return from pharmaceutical innovation” 2014

¹⁶ Paul, S.M., “How to improve R&D Productivity: The pharmaceutical industry’s grand challenge”, 2010

¹⁷ Danzon, P. “The economics of the biopharmaceutical industry” 2010

634 in what relates to hospital drugs and even higher for areas like oncology (743 days) or orphan drugs (718 days)¹⁸.

The definition of the price for a new drug is another of the burning issues in Portugal, in Europe and around the world due to the external reference pricing systems. According to recent studies¹⁹ all countries in Europe use some form of external reference pricing. Portugal chose to use this methodology in order to control costs related to pharmaceutical expenditure. This method consists on creating baskets of countries where a product is sold and setting the price for a new country taking into consideration the prices already in place in the reference countries. To reduce prices on its own country, countries tend to select for their basket reference countries with low prices. But this method has a major setback. With this methodology a change in the price of a country impacts the global market. For example, a country like Portugal has in its basket 3 countries (Spain, France, Slovenia) and serves as reference for 2 major markets like Brazil and Turkey²⁰, meaning that the definition of a price in Portugal is crucial for pharmaceutical countries as it may affect their sales worldwide.

In Portugal, the pharmaceutical market reached its peak in 2009, with revenues for the sector worth 4.347 Million Euros²¹. About 23% (997 Million) related to hospital market and the remaining 77% related to ambulatory (3.350 Million). By 2012 the market shrunk to a total of 3.621 Million Euros, mainly due to a reduction in the ambulant market. A total contraction of 17% in the pharmaceutical market since 2012, due to factors like the review of the basket of reference countries, the review of the margins along the supply chain in the ambulant market, the entry of new generics and the review of its commercialization prices, the introduction of electronic prescription or the introduction of the obligation to prescribe using the international non-proprietary names (INN) of drugs. It is also relevant to state that the reduction on the market value didn't correspond to a reduction on volume. In 2009 it were sold 259,9M drug packages against 275,3M in 2012.²²

With the entry of Troika in 2011 it was also introduced a cap in the total expense related to pharmaceuticals, in a form of an annual agreement celebrated between the pharmaceutical industry and the Ministry of Health. In 2012 the agreement set the pharmaceutical expenditure supported by the NHS to 1,25% of the GDP (estimated in 168B euros)²³, resulting in a reduction of 300 Million euros in pharmaceutical expenditure in what compares to 2011 (170 Million related to hospital market and 130 Million related to ambulatory).

¹⁸ Felix, J., EXIGO – “Pharmaceutical drugs public financing in Portugal 2007-2011”

¹⁹ RAND, “The use of External reference pricing”, 2013

²⁰ APIFARMA, “Pharmaceutical industry in numbers 2013”, based on INFARMED data

²¹ APIFARMA, “Pharmaceutical industry in numbers 2013”, based on INFARMED data

²² APIFARMA, “Pharmaceutical industry in numbers 2013”, based on INFARMED data

²³ INE, GDP, current prices, 2012

4. Pfizer

Pfizer Inc. is one of the world's largest pharmaceutical companies with total sales of \$59.0 billion worldwide in 2010, created in the 19th century in the US. Like any other pharma company a major cut of its budget is dedicated to R&D, rounding \$7.9 billion (13% of revenues). It has a total workforce of more than 80,000 people²⁴ spread throughout more than 90 countries. Besides the pharmaceutical business, the core of the company, Pfizer also has a consumer healthcare unit (dedicated to OTC products) as well as a unit dedicated to animal health, Zoetis.

Pfizer always had a growth strategy that included besides internal growth, the realization of relevant acquisitions. Back in 2003 Dr. John LaMattina, president of Pfizer Global Research and Development, described the three main foundations on which Pfizer relied on: “*increasing productivity, leveraging scale, and adding value through collaborations, partnerships and acquisitions*”. Pfizer’s major acquisition was performed in October 15, 2009, when Pfizer acquired Wyeth, one of the major biotech companies worldwide. Fold Rx was acquired a year after, on October 6 2010 by around \$400M²⁵.

In terms of its major products, Pfizer has a wide portfolio, covering several therapeutic areas, with its main strengths in the cardiovascular domain. In 2012, Lyrica, Lipitor, Enbrel, Prevenar 13, Celebrex and Viagra delivered more than \$2 billion each in revenues worldwide, while Norvasc, Zyxon and Sutent each surpassed \$1 billion each.

In 2012 Pfizer suffered a deep reduction on sales due to the loss of exclusivity of its top selling drug, Lipitor, what increased the pressure to obtain results from other products and new deals. With the close to the loss of exclusivity of its main products Pfizer had already started to refocus its R&D in other areas with higher profitability like cancer and biotechnology drugs.²⁶

Pfizer’s main market continues to be the US, where their main headquarters are located, but the European market is also quite relevant for the company representing around 25% of Pfizer’s sales in 2010. Major countries in Europe for Pfizer are UK, France, Germany, Italy and Spain.

In Portugal, like the majority of the international pharmaceutical companies, Pfizer’s structure is mainly dedicated to marketing & sales, along with smaller structures related to R&D (medical) and market access. There is no local production of drugs.

²⁴<http://www.fiercebiotech.com/press-releases/pfizer-expands-its-generics-portfolio-through-innovative-licensing-deals-increasing-a> – accessed 08/2015

²⁵ Management report Pfizer, 2012

²⁶ <http://www.wikinvest.com/wiki/Pfizer> – accessed 08/2015

5. Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP)

TTR-FAP is known as “*paramiloidose*” or “*doença dos pezinhos*”, a rare disease that affects between 8.000 – 10.000 people around the world²⁷. Prevalence in Europe is 1,1 per 100.000²⁸. The disease was discovered by Corino de Andrade, a Portuguese neurologist in 1939²⁹. This is a chronic, neurodegenerative, hereditary disease that usually manifests in young adults when they are around their 30s and progresses during 10-15 years leading to patients’ death³⁰. However, there are cases reported by physicians where the disease started earlier, 19 yo., and later, 80 yo.

TTR-FAP is one of the 3 types of existing familial amyloid polyneuropathy (FAP) and is a genetically inherited disease that passes from parents to their children with a probability of vertical transmission of 50%³¹. TTR-FAP patients have a mutation in a protein, transthyretin (TTR) that is mainly synthesized in the liver³². The mutation in this protein causes the deposition of amyloid fibrils in the nerves and in the heart affecting the normal function of the organs, causing nerve damage and increasing the possibility of premature heart failure³³.

This disease is highly disabling causing sensory motor neuropathy, including pain and weakness in the lower limbs, as well as an experience of gradual loss of sensation. It can also affect the kidneys causing renal failure. In later stages it may also cause erectile dysfunction, weight loss and urinary incontinence, and also impacts the digestive system. This disease has a high impact in terms of the patient’s quality of life. With the progression of the disease, around 5-9 years after diagnosis, patients lose their ability to walk, become bedridden and unable to take care of themselves, before reaching the terminal stage, death³⁴.

From the social point of view this disease impacts not only the patients, but also their families. These patients have several care needs, namely in more advanced stages when they become bedridden. The families have to live with the shadow of the disease from the beginning. As it is genetically inherited parents have several doubts on having children, with the fear they might pass the disease to them. By law it is not possible to make tests to know whether the children are infected until they reach majority (18 yo). Amniocentesis is only performed if there is risk to the baby, as the baby that will be born even if carries

²⁷ Ando Y *et al.* Guideline of transthyretin-related hereditary amyloidosis from clinicians. *Orphanet Journal of Rare Diseases*. 2013;8:31

²⁸ INFARMED, “Tafamidis hospital use - Reimbursement report”; 2012

²⁹ GAP – Boletim nº1 - 2007

³⁰ Ando Y *et al.* Guideline of transthyretin-related hereditary amyloidosis from clinicians. *Orphanet Journal of Rare Diseases*. 2013;8:31

³¹ Sekijima Y, Yoshida K, Tokuda T, Ikeda S. Familial transthyretin amyloidosis. In: Pagon RA, Bird TD, Dolan CR, Stephens K, eds. GeneReviews [Internet]. Seattle, WA: University of Washington; 1993–2009

³² Hou X, Aguilar M-I, Small DH. Transthyretin and familial amyloidotic polyneuropathy: recent progress in understanding the molecular mechanism of neurodegeneration. *FEBS J*. 2007; 274:1637-1650.

³³ Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve*. 2007;36:411-423

³⁴ Coutinho P, da Silva AM, Lima JL, Barbosa AR. Forty years of experience with type 1 amyloid neuropathy: review of 483 cases. In: Glenner GG, e Costa PP, de Freitas AF, eds. Amyloid and Amyloidosis. Amsterdam: Excerpta Medica; 1980:88–98.

the disease may be healthy till their 30s. Most families have several members with TTR-FAP and that has a high impact on the relations and the family living.

a. TTR-FAP in Portugal

Portugal, and specifically the northern region, is one of the 3 main endemic zones of TTR-FAP worldwide, other two are Sweden and Japan. In Portugal this rare disease's prevalence is higher than 2/100.000³⁵, and there are at least 600 independent families identified where at least a family member has TTR-FAP³⁶. Prevalence of symptomatic TTR-FAP in Portugal is around 2.000 patients and other 6.000 asymptomatic that may transmit the disease without knowing it. National incidence rounds 100 new cases every year. Main focus of the disease is in the municipalities of Póvoa do Varzim and Vila do Conde, where there are at least 6-8 new families with reported cases of TTR-FAP every year.

In countries like Sweden the disease is asymptomatic in more than 50% of the cases³⁷, but in Portugal it is reported by specialists has being more symptomatic, and therefore having higher impact on health and health quality of patients. Since this is a rare disease where Portugal is one of the most affected countries, it has always been a lot of pressure around it in the society and in the medical society: what are the causes of such a disease? Methods to diagnose? How to treat it and how to ensure a better quality of life to patients and their families?

In Portugal there are two main patient organizations related to TTR-FAP. In 1979 it was created the "Associação Portuguesa de Paramiloidose" (APP), with headquarters at Vila do Conde, in the northern region of Portugal, probably one of cities in the world most affected by this disease. It was created by a group of patients, family members, physicians and other healthcare professionals to support the patients namely in terms of their healthcare, transportation and social support. This is the main TTR-FAP association in Portugal, and is still active today. In 2007 it was created the "Grupo de Apoio à paramiloidose", another platform more dedicated to the promotion of the disease and its impacts, the need for new treatments, and to support scientific research. Other associations like "Raríssimas", related to several rare diseases in Portugal, also supported TTR-PAF patients and their fight in the access for new treatments.

³⁵ INFARMED, "Tafamidis hospital use - Reimbursement report"; 2012

³⁶ Sousa A, et al. "Genetic epidemiology of familial amyloidotic polyneuropathy (FAP)-type I in Póvoa do Varzim and Vila do Conde (north of Portugal). Am J Med Genet" 1995;60:512-521, p. 513 and p. 517

³⁷ <http://paramiloidose.no.sapo.pt/paramiloidose.html>

6. Orphan drugs & Vyndaqel (INN Tafamidis)

Before 2011 there were no treatments for TTR-FAP other than liver transplant. Liver transplantation started to be performed in Portugal in 1992 in the Hospital Curry Cabral, in Lisbon. The transplantation halted disease progression in most patients but had high costs due to high morbidity/mortality rates³⁸ and patients had to wait in a long liver transplant queue before being approved. When, in 2011, Vyndaqel (INN – Tafamidis) was approved by the European Medicines Agency (EMA) ³⁹, a Pfizer pharmaceutical drug with indication for “the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment”, a new hope arose for TTR-FAP patients and their families.

According to the European Medicines Agency, orphan drugs, like Vyndaqel, have specific criteria to be designated as such. They must cumulatively be intended for the treatment, prevention or diagnosis of life-threatening or chronically debilitating disease and prevalence lower than 5 per 10.000 in the EU. When approved, an orphan drug benefits from specific incentives “including protocol assistance, scientific advice specific for designated orphan medicines, and market exclusivity once the medicine is on the market per a period of 10 years”⁴⁰. This last topic is quite relevant because as this drug is only indicated to a small population there is the need to assure that the revenue generated by its sales justifies the investment made⁴¹, so that pharmaceutical companies continue to invest in these niche markets.

This new product was a major breakthrough in the life of TTR-FAP patients as it had the ability to stabilize transthyretin and thereby inhibit amyloid formation and the disease progression (EMA 2011).

Fold Rx, the biotech company that developed the product submitted the first registry to the European Medicines Agency in 2006. After that they developed several clinical trials. The main clinical trial that supported the product's safety and clinical efficacy was the phase III double blind trial Fx-005⁴². Started in 2007 and went till 2009, comparing Vyndaqel against placebo in an 18 months trial. The study main endpoint was the evaluation of the Neuropathy Impairment Score of the Lower Limb (NIL-LL) that was performed by a physician in order to evaluate disease progression. 91 patients completed the study duration and the results were statistically significant ($p=0,041$). The proportion of patients who experienced no deterioration in neurological impairment (no progression of neurodegeneration) was higher in the Vyndaqel population. 60% against 38% in placebo population. In order to confirm this evidence 86 out of the 91 patients enrolled in a sub sequential 12-month, open-label extension study that evaluated the long-term safety, tolerability, and efficacy of Tafamidis, where all patients were now treated

³⁸ Plante-Bordeneuve V, Said G. “Familial amyloid polyneuropathy”. *Lancet Neurol* 2011; 10:1086-97.

³⁹ EA/CHMP/546201/2011

⁴⁰ <http://www.ema.europa.eu/> – accessed 08/2015

⁴¹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp – accessed 08/2015

⁴² EMA, “Vyndaqel assessment report”, 2011

with Vyndaqel 20 mg once daily. This study concluded that Tafamidis was safe and well tolerated over 30 months (18+12). The effect of Tafamidis in slowing neurologic progression and preserving QOL was sustained over this time. Moreover patients who started Tafamidis earlier had less neurologic impairment at 30 months than those who started treatment after an 18-month delay (were taking placebo in the first trial), supporting the value of the early initiation of this disease-modifying approach⁴³. There were no other evidences to support the products efficacy over a longer period of time.

7. The deal

The deal between Pfizer and the NHS that would decide whether the product would be reimbursed and therefore available for patients was crucial all parties, but above all was crucial for the patients and their families.

Public pressure was high. In 2011 and early 2012 there were riots and vigils in front of the Ministry of Health and other Health facilities, like the Hospital Santo António, in Oporto, where the majority of the Portuguese patients were being followed. These initiatives were performed by patients, families, patient associations and health professionals. At this level it stood out from the crowd the effort and the role of the main TTR-FAP patient association in Portugal: Associação Portuguesa de Paramiloidose (APP). After the publication of the phase III trial results from Tafamidis in 2009 this association performed several initiatives to assure patients access to this innovative life-saving drug. The news about Tafamidis and its results spread-out very quickly since the phase III trial counted with several Portuguese patients amongst the study population. The patients in the study were the first to ever have access to Tafamidis and would have the drug assured until the product's commercialization, as that is one of the main directives regarding clinical trials in humans⁴⁴. If results show safety and efficacy the pharmaceutical company is ethically obliged to provide the innovative drug to patients even after the end of the trial. So patients were not only reading about the results of this new drug, they also knew other patients that were actually "feeling the results". The pressure of patients and their families was huge over APP. Nurse Carlos Figueiras, President of APP, stated that they "*received several daily calls, day and night, to know whether the association had any news regarding drug financing and what could be done to speed it up*".

Amongst other initiatives, in 16 of October 2010 APP organized the 1st congress related to TTR-FAP. The celebration of a day dedicated to this disease was a relevant initiative in the plan to fight this disease. That day would serve to increase public's awareness over this disease. TTR-FAP was known to most of the Portuguese population as "doença dos pezinhos", but like other rare diseases it was not in the top of mind of their concerns, and therefore in the top of mind of health authorities. The creation of a day

⁴³ Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy

⁴⁴ Law Decree n.º 21/2014 – Clinical research - Article 23

specifically dedicated to the disease would bring more information to the public since some of the initiatives and events would be covered by the media.

From 2009 onwards APP developed several contacts with the stakeholders related to Tafamidis access process. APP made their first rounds of contacts with the Socialist government (PS) and, after 2011 with the change of government, with the social democrats (PSD). They also had contacts with other relevant entities in the evaluation process of reimbursement regarding Tafamidis, namely INFARMED (drug regulatory entity) and ACSS (Central Administration of the Health System). The first was a critical stakeholder in the process, as the decision of reimbursement regarding hospital drugs lied in their field of responsibility, whereas the decisions regarding ambulatory drugs were in the hands of the Ministry of Health that periodically published a list of the reimbursed drugs.

The main issue with Vyndaqel was related to its price. During the evaluation period regarding Vyndaqel's reimbursement in Portugal the product was approved in other countries, where the number of patients and the budget impact was lower. The price in France for this product was public; roughly 135k euros per patient/year. In Portugal the proposal on the table was to acquire the drug for all patients that met the specific criteria set by the clinical body. According to interviews it was estimated that in the first year 240 patients would start medication in Hospital Santo Antonio, in Oporto, and 40 others would start in Hospital Santa Maria, in Lisbon.

On the industry side the first negotiations that occurred were made with Fold Rx's responsible. Portugal was a "natural" market for the product due to the high prevalence registered, so they rapidly approached the relevant authorities with the early results from the clinical trials. After Fold Rx's acquisition Pfizer's management team took charge in the front seats of the negotiation with the Ministry of Health and relevant authorities. Pfizer's message was clear. They had an innovative drug with proven results to reduce disease progression of TTR-FAP, a highly incapacitating disease with a relevant prevalence in Portugal. The patients had to have access to their drug as it had proved its high added value. Like the any other innovative drug, the price was being proposed based on this premise. It was on the Ministry of Health's hand to save this population.

The NHS had the obligation to analyse the relevance and benefits of this innovative drug. INFARMED was the entity that played the major role in this evaluation as they were entitled to analyse the robustness of the trials namely in terms of the population, methodology used and benefits (safety, therapeutic value added and economic value). As TTR-FAP is a rare disease there was the need to take that fact into consideration in terms of the number of patients included in the study and the validity of the results on the long term. Regarding the economic evaluation there was the need to analyse the burden of disease and its economic impact in the long term, in order to compare costs and benefits of using Vyndaqel vs. standard care. On the Ministry of Health's side was the politics decision regarding whether there should be additional allocation of budget to this disease. Even with positive results in terms of clinical and

Vyndaqel (Tafamidis) - Market entry in Portugal

economic value there was the need to understand if Portugal had the capability to pay for it, and if so how should it be made.

The financing model relayed on the ACSS side. There were several types of deals that could be used to formalize the financing model of hospitals, who would acquire this drug from Pfizer. The regular option would be to include it under the annual hospital contract ("*contrato de gestão*") celebrated between each Hospital and ACSS, meaning that the payment related to this treatment would be made by DRG (diagnosis related group) and the allocation of the fee for this disease would flow to the hospital budget in one of the current production lines, there would be no specific allocation of budget to Vyndaqel.

Alternatives were other models like vertical financing or risk sharing agreements. With vertical financing it was created a specific line of financing in the annual hospital contract, with the amount estimated under a price-volume agreement, meaning that the fees allocated to the treatment of TTR-FAP patients could only be used to that end. This type of agreement was already being used in other therapeutic areas with high cost drugs, like infectious diseases, namely HIV. Risk Sharing agreements and other patient access schemes where the pharmaceutical industry was reimbursed based on outcomes rather than in volume were also starting to be implemented in Europe, namely in Italy, but had never been used in Portugal.

Patients, families and patient associations were on the streets demanding for access to Vyndaqel and its life saving results. Patients had suffered the effects of TTR-FAP for too long. The media was covering the story, increasing the pressure on the parties. Physicians wanted alternative ways to treat their patients with better results. Pfizer and the NHS were being pushed to close the deal, but there was still a gap between the parties. Price definition was one of the main variables on the table as it impacted, on one hand, Pfizer results and, on the other hand, NHS's ability to pay for the drug in the short and long term.

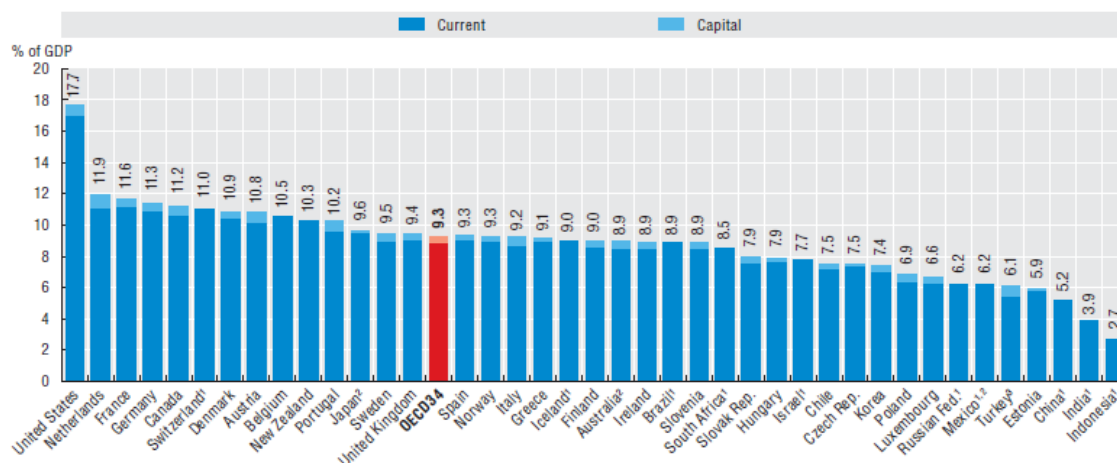
Compromises would have to be made; bridges would have to be done.

8. Questions

- i. Why was the introduction of Vyndaqel in the Portuguese market so relevant for Pfizer?
- ii. What should NHS take into consideration when analysing the reimbursement decision?
- iii. What were the positions and arguments of each party (NHS vs. Pfizer) in the deal regarding Vyndaqel's reimbursement?
- iv. What was the role of the patient's associations and the media in the process? Was it good for the deal?
- v. Which method should the NHS use to acquire Vyndaqel?

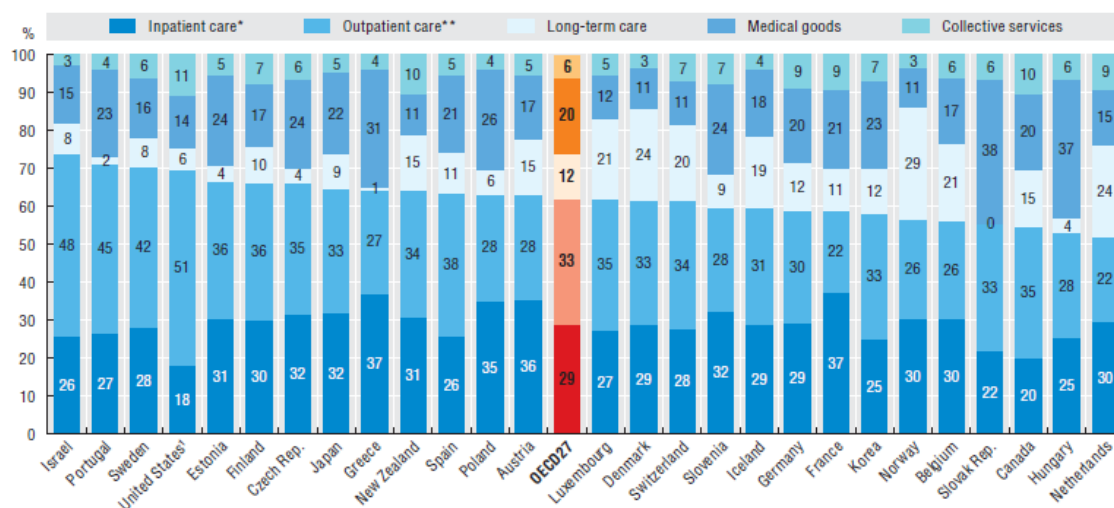
9. Annexes

1 – Health expenditure as a share of GDP, 2011

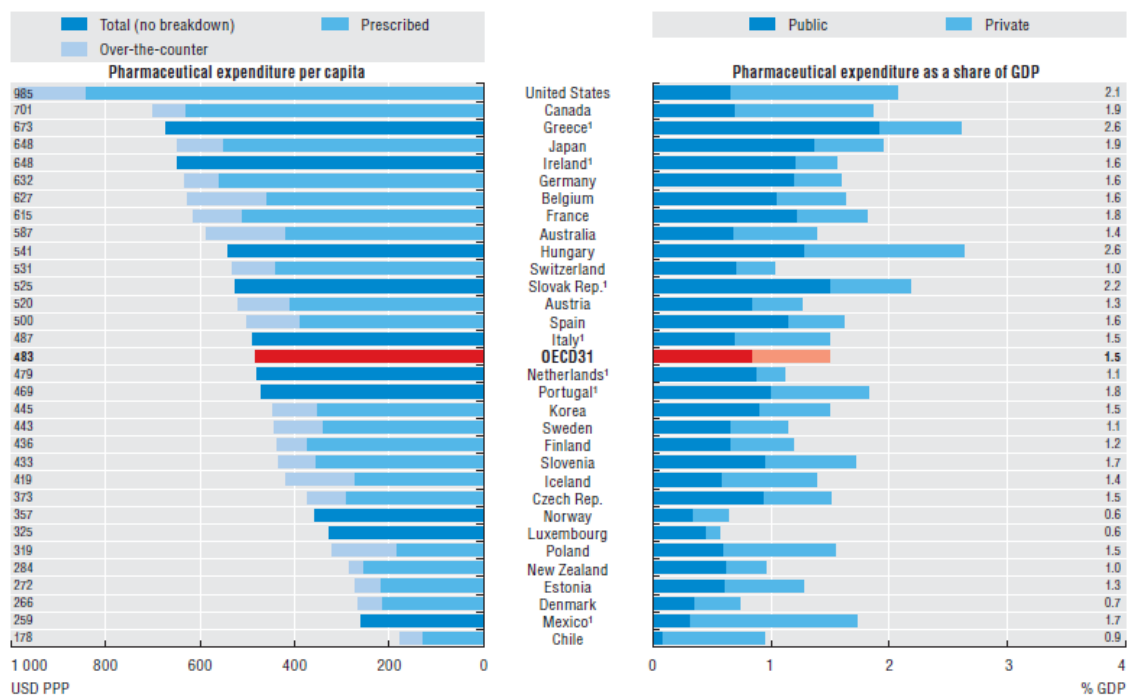


2 – Current health expenditure by function of health care, 2011

7.3.1. Current health expenditure by function of health care, 2011 (or nearest year)



3 – Expenditure on pharmaceutical per capita and as a share of GDP, 2011

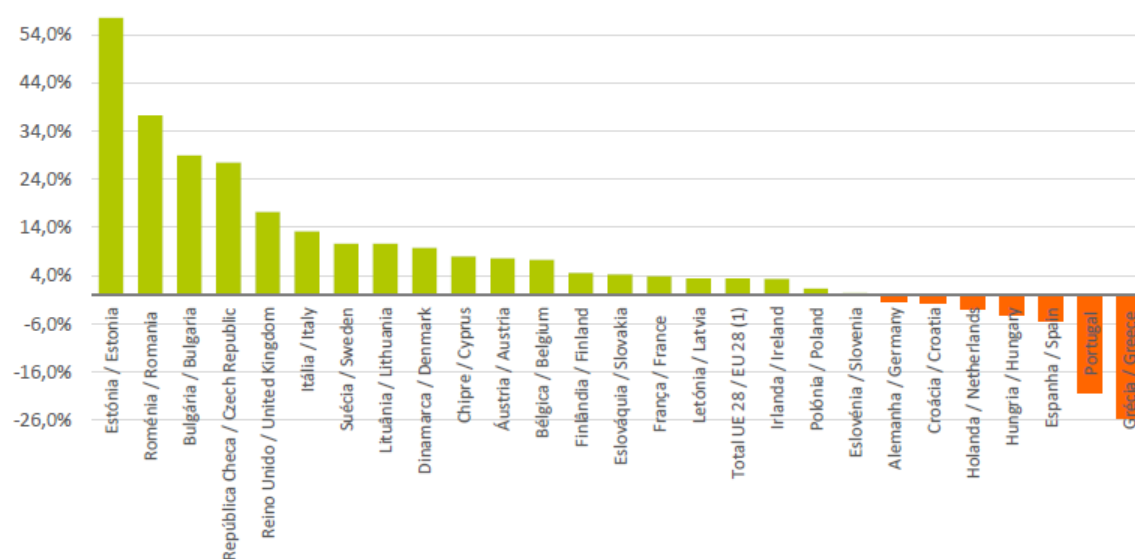


4 – Portugal – Pharmaceutical total market value (retail price)

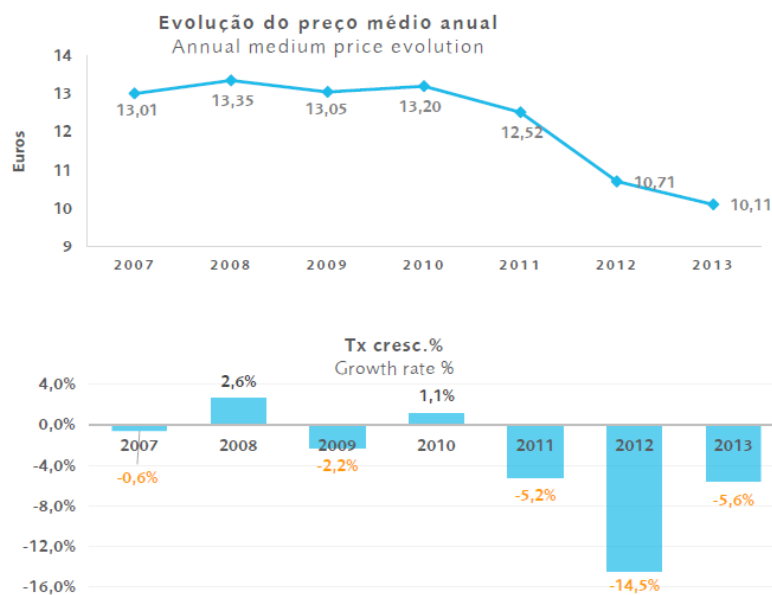
Unidades: Milhões de euros; % / Units: Million euros; %

Anos Years	Mercado Total (1) Total Market	V.H..% Growth %	Mercado Ambulatório (2) Ambulatory Market	V.H..% Growth %	Quota (%) Share %	Mercado Hospitalar Hospital Market	V.H..% Growth %	Quota (%) Share %
2008	4.268	3,0%	3.372,2	2,2%	79,0%	896,0	6,2%	21,0%
2009	4.347	1,9%	3.350,0	-0,7%	77,1%	997,3	11,3%	22,9%
2010	4.295	-1,2%	3.266,5	-2,5%	76,1%	1.028,1	3,1%	23,9%
2011	3.995	-7,0%	2.973,3	-9,0%	74,4%	1.021,6	-0,6%	25,6%
2012	3.621	-9,4%	2.632,3	-11,5%	72,7%	988,7	-3,2%	27,3%

5 – Total pharmaceutical market in Europe – Growth 2008/12



6 – Annual medium price evolution in the Portuguese pharmaceutical market and growth rate



Vyndaqel (Tafamidis) - Market entry in Portugal

7 – Pfizer Inc. revenues by segment and geographic area (2010-2012)

The following table provides Worldwide revenues by operating segment, business unit and geographic area:

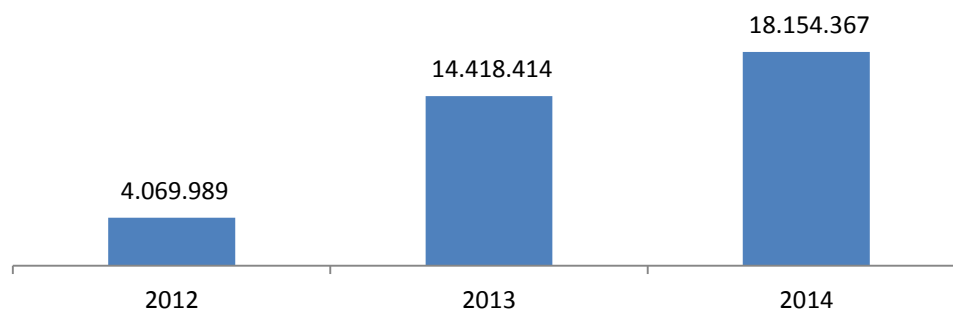
(MILLIONS OF DOLLARS)	Year Ended December 31,									% Change					
	Worldwide			U.S.			International			Worldwide		U.S.		International	
	2012	2011 ^(a)	2010	2012	2011 ^(a)	2010	2012	2011 ^(a)	2010	12/11	11/10	12/11	11/10	12/11	11/10
Biopharmaceutical revenues:															
Primary Care Operating Segment	\$ 15,558	\$ 22,670	\$ 23,328	\$ 8,191	\$ 12,819	\$ 13,536	\$ 7,367	\$ 9,851	\$ 9,792	(31)	(3)	(36)	(5)	(25)	1
Specialty Care	14,151	15,245	15,021	6,206	6,870	7,419	7,945	8,375	7,602	(7)	1	(10)	(7)	(5)	10
Oncology	1,310	1,323	1,414	573	391	506	737	932	908	(1)	(6)	47	(23)	(21)	3
SC&O Operating Segment	15,461	16,568	16,435	6,779	7,261	7,925	8,682	9,307	8,510	(7)	1	(7)	(8)	(7)	9
Emerging Markets	9,960	9,295	8,662	—	—	—	9,960	9,295	8,662	7	7	—	—	7	7
Established Products	10,235	9,214	10,098	4,738	3,627	4,501	5,497	5,587	5,597	11	(9)	31	(19)	(2)	—
EP&EM Operating Segment	20,195	18,509	18,760	4,738	3,627	4,501	15,457	14,882	14,259	9	(1)	31	(19)	4	4
	51,214	57,747	58,523	19,708	23,707	25,962	31,506	34,040	32,561	(11)	(1)	(17)	(9)	(7)	5
Other product revenues:															
Animal Health	4,299	4,184	3,575	1,771	1,648	1,382	2,528	2,536	2,193	3	17	7	19	—	16
Consumer Healthcare	3,212	3,028	2,748	1,526	1,490	1,408	1,686	1,538	1,340	6	10	2	6	10	15
Other operating segments	7,511	7,212	6,323	3,297	3,138	2,790	4,214	4,074	3,533	4	14	5	12	3	15
Other ^(b)	261	300	319	81	88	103	180	212	216	(13)	(6)	(8)	(15)	(15)	(2)
Total Revenues	\$ 58,986	\$ 65,259	\$ 65,165	\$ 23,086	\$ 26,933	\$ 28,855	\$ 35,900	\$ 38,326	\$ 36,310	(10)	—	(14)	(7)	(6)	6

Legend: SC&O – Specialty care & Oncology; EP&EM – Established product & Emerging Markets

8 – Pfizer Inc. stock market share price evolution



9 – Costs reported with Tafamidis, NHS Portugal (euros)



10 – Pfizer investment related to partnerships with Patient Associations related to TTR-FAP, in Portugal

Beneficiary	Description	2009	2010	2011	2012	2013
Associação Portuguesa de Paramiloidose	Core funding				50.000	-
	TTR-FAP National Day				60.000	25.000
	Newsletters and support to awareness initiatives regarding TTR-FAP				10.000	35.000
Raríssimas	Core funding	1.700	15.000	28.000	17.500	12.750
Total		1.700	15.000	28.000	137.500	72.750
% Total support		0%	7%	9%	46%	42%

11 – Public Petition submitted to the Parliament, to request Tafamidis approval, 2011



Comissão de Saúde

I – Nota Prévia

A presente Petição, subscrita por 9404 assinaturas e da iniciativa de Sérgio Guimarães Tomaz, deu entrada na Assembleia da República, a 21 de Setembro de 2011 e, tendo sido admitida, foi a mesma remetida no mesmo dia para a Comissão Parlamentar de Saúde, para apreciação e elaboração do respectivo parecer.

II – Conteúdo e objecto da Petição

Os peticionários pretendem, com esta iniciativa, que sejam tomadas as medidas adequadas para que os portadores de paramiloidose, em fase inicial da doença, possam iniciar o seu tratamento com tafamidis. Solicitam também que seja permitida a execução do disposto na lei no que se refere a uma autorização especial e que a nenhum cidadão seja negado o direito à saúde por razões económicas.

12 – Several news, published in the media related to initiatives to request Tafamidis approval, 2011

Uma petição, milhares de vidas

Por ANA BACALHAU*

Aqui há umas semanas, chegou-me ao conhecimento a petição pelo fim da paramiloidose, que pretende a prescrição clínica em Portugal de um medicamento que ajuda no controlo da polineuropatia amiloideótica familiar, ou paramiloidose, conhecida como “doença dos pezinhos”.

Conheço bem esta doença degenerativa e fatal, que ataca pessoas na flor da idade, deixando cônjuges e filhos em luto pela sua perda. Outra das absolutas maldades da paramiloidose é que é hereditária, sendo que a probabilidade de a mesma passar de pais para filhos é de 50%. Então, temos os filhos que assistiram à morte lenta dos pais a sofrer pela possibilidade de se verem a si mesmos nas mesmas condições. Desde há algum tempo, o transplante hepático tem sido a única terapêutica possível, atrasando a progressão da doença, mas trazendo consigo a angústia da espera, o medo de não se sobreviver... Há uns anos, tem estado em estudo um medicamento que impede a evolução da doença, tendo sido aprovado recentemente pela European Medicines Agency. O Tafamidis, como é chamado, espera autorização de distribuição no nosso país. O objetivo desta petição é o de pressionar as autoridades e a classe política para que se traga o Tafamidis para Portugal o mais rapidamente possível. Já perdi pessoas de quem gostava muito para a doença e já perdi pessoas de quem gostava muito para o transplante. Não quero perder mais.

Se existe outra terapêutica, menos traumática, mais segura e mais barata que o transplante hepático, então esta petição tem o meu total apoio. Se, de alguma forma, forem sensíveis também aos seus argumentos, procurem-na em www.peticaopublica.com. Não pode haver mais ses, apenas e só assim.



*Camora

Data: 2011/10/23 DIÁRIO DE NOTÍCIAS - PRINCIPAL
Título: Doentes reclamam por medicamento
Tema: Saúde
Periodicidade: Diária
Temáticas: Geralista

Doentes reclamam por medicamento

PARAMILOIDOSE Doentes com paramiloidose juntaram-se ontem, em Vila do Conde, reclamando dos governantes o “direito à vida” e a disponibilização do *Tafamidis*, um medicamento que evita o transplante hepático. Nos cartazes podia ler-se “basta de morrer com paramiloidose” ou “em Portugal também se condena à morte”.

Jornal da Associação Portuguesa de Paramiloidose

“TAFAMIDIS” (FX - 1006 A) - Testemunhos

No dia 16 de Junho de 2010, durante a Campanha de Dia Nacional de Luta Contra a Paramiloidose, todo o besta auditório presente no Hospital de Santo António, incluindo o Secretário de Estado Adjunto e da Saúde, Dr. Manuel Pizarro, ouviram Pedro Oliveira, falar sobre o Medicamento “TAFAMIDIS” e afirmar com um sorriso nos lábios e os olhos a brilhar de alegria, que o “TAFAMIDIS” lhe salvou a vida e que este encontro representava a vida.

Em Portugal 45 portadores da (PA) estão desde o ano de 2007 a tomar este Medicamento, no prolongamento do mesmo realizado, senão os custos suportados pela Farmacêutica Americana (FalkRx).

A APP tem conhecimento que o “TAFAMIDIS” não traz efeitos secundários significativos e como o Pedro Oliveira, outras portadoras se gem tomam o Medicamento e não estão à espera do Transplante Hepático.

Vários testemunhos comprovam que o “TAFAMIDIS” pode ser a diferença entre a “Vida e a Morte”.



Tem futuro maravilhoso a quem de nós tem tomado este medicamento já possui um futuro brilhante, para a vida.



Foi o Sr. Pedro Oliveira, na Dia Nacional de Luta Contra a Paramiloidose, no Hospital de Santo António - Porto, testemunha que o Medicamento Tafamidis lhe salvou a vida.

Portugal



A actriz Sónia Brazão foi acusada pelo Ministério Público (MP) do crime de libertação de gases sufocantes e de explosão. O despacho foi proferido na segunda-feira pelo MP e resultou na acusação da actriz por este crime, cuja modalidade penal pode atingir os oito anos de prisão.

Doentes com paramiloidose cercam gestão de hospital

Pacientes reclamam medicamento novo que lhes poderia evitar transplante hepático

Quatro doentes com paramiloidose, a “doença dos pezinhos”, concentraram-se durante o dia de ontem à porta da administração do Hospital de Santo António, no Porto, na tentativa de convencer os responsáveis a

disponibilizar-lhes um novo medicamento que pode evitar o transplante de fígado, até agora a única hipótese de sobreviverem a esta doença fatal.

O adjunto da direcção clínica recebeu-os pela manhã. “Disse que estamos a pressionar a entidade errada, que só quando houver autorização de introdução no SNS (já cargo da Autoridade Nacional do Medicamento, o Infarmed) poderemos fornecer”, lamentou José Manuel Correia, 29

anos, que decidiu ficar no interior do hospital até ter outra resposta. “Disse não saímos, estamos em desespero absoluto”, garantiu à tarde, inconformado, este homem que vê a sua situação clínica deteriorar-se de dia para dia. Só saiu depois de o administrador do hospital ter admitido, em conferência de imprensa, que a unidade “não tem dinheiro” para tratar os mais de cem doentes ali seguidos. O passo seguinte, anunciou, vai ser

“pressionar o Ministério da Saúde”. O Tafamidis foi recentemente aprovado pela Agência Europeia do Medicamento e, enquanto o processo de avaliação para fixação de preço e comparticipação estatal decorre entre o Infarmed e o laboratório, os hospitais podem pedir, caso a caso, autorização de utilização especial (AUE) do fármaco, explicou ao PÚBLICO um responsável do Infarmed. O Infarmed, aliás, já aceitou dois

pedidos de AUE deste remédio, cujo custo anual por paciente ronda os 125 mil euros. José Correia tem um pedido de AUE assinado pelos seus médicos que aguarda acção da administração do hospital. O problema é que o Santo António concentra o grupo dos doentes com indicação para usar o remédio (cerca de 120 num total de 170 no país) e aceitar tantas AUE representaria uma despesa enorme. Alexandra Campos

Pedagogical Case Study

Vyndaqel (Tafamidis) – market entry in Portugal

Teaching notes

Author – Hugo José Macedo Pedrosa

Supervisor – Professor Pedro Pita Barros

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1. Pedagogical objectives of the case

This case is structured as a pedagogical case study. The main topic addresses the market entry of Tafamidis in Portugal, an orphan innovative drug. It is analysed the context, the facts and the procedures that were followed to assure that the product would obtain reimbursement and therefore would be available for patients. Like any other innovative product, Tafamidis market entry process had several challenges along the way, namely due to the high price of the product, where there is a conflicting view regarding value from the point of view of the pharmaceutical industry and the point of view of the payer.

This case was selected since it is one of the most relevant cases regarding pharmaceutical drugs introduction in the Portuguese market, that happened in a difficult context for all stakeholders, and that had a wide media coverage. The access of patients to innovation, and in particular to therapeutic innovation, is one of the most relevant topics in health, in Portugal and around the world, currently.

The student case regarding Tafamidis market entry is based on real events that were collected using desk research and direct interviews with the main stakeholders involved in the process. The case has the following structure:

- Chapter 1 starts by presenting the challenge of bringing Tafamidis to the market from Pfizer's point of view. It is made a brief contextualization on the main case highlights.
- On chapter 2 there is a high level analysis of the Portuguese healthcare system and its particularities, so that students can understand the market environment at the time of the market entry of the product.
- Chapter 3 focuses on market access in terms of the challenge of bringing a new drug to the market, and highlights some of the specificities of the Portuguese market.
- Chapter 4 analysis Pfizer's momentum at the time of Tafamidis launch in order to contextualize the company and understand what was at stake at the time.
- Chapter 5 contextualizes the disease, Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP), so that the students get a general understanding on the disease's context, its impact in the patients and their families, its prevalence, the treatments available prior to Tafamidis and the specific context of TTR-FAP in Portugal.
- Chapter 6 introduces Vyndaqel, and presents the clinical relevance of this innovative drug.
- Finally in chapter 7 it is presented the context regarding the deal between Pfizer and the Ministry of Health (MoH) that would bring the product to the market.
- Chapter 8 presents the questions for discussion in class.

Along the analysis of the case there are several relevant aspects regarding the process of Tafamidis marketing approval and reimbursement process that are analysed in detail in order to learn with the experience of this case. In the scope of this thesis it were selected the following themes, as the most

relevant, and that should be addressed and used from a pedagogical point of view. These themes are directly linked to the questions posed to the students in chapter 8, and will allow discussion around:

- **Price referencing schemes in hospital markets (question i & ii)** – How do these schemes work? Where are they applied and how do they affect the markets, and the access to drugs? What is international reference pricing?
- **Negotiations between pharmaceutical companies and the national bodies of authority (questions ii & iii)** – What are the main arguments presented by the parts? What are the concerns of each stakeholder? How to align and reach consensus to finalize deals?
- **Influence of Media in the market entry of pharmaceuticals (question iv)** – What is the role played by the media in the market launch of new products? What is their influence in the outcome of the negotiation?
- **Influence and relationship between patient's associations and the pharmaceutical industry (question iv)** – What is the relation between pharma companies and patient associations? What do they stand for? What types of action are performed by the associations? What is their impact?
- **Financing and contracting hospital drugs (question v)** – What are the most used drug financing methodologies? What are the alternatives and new trends? How to select the appropriate methodology? Are there specific conditions for orphan drugs?

The teacher note presents the pedagogical objectives of this case, and the

2. Methodology

This thesis was developed under the supervision of Professor Pedro Pita Barros. It were used two main sources of information. Regarding secondary data sources it was made an exhaustive search using the main specialty search engines (PubMed and Google scholar) regarding the Tafamidis case, market access, orphan drugs and market entry context in Portugal and Europe. Information was analysed and included along the student case and teacher notes.

Regarding primary data collection it was decided that in order to have a deeper understanding of the Tafamidis case, and as only some of the information was of public knowledge, the best approach would be to perform individual interviews with the main stakeholders involved in this case. Below is presented a list of the 7 interviewees that accepted to participate, and that allowed the development of this case. They presented different but complementary points of view on Tafamidis market entry process. Pfizer's representatives were invited to participate, but that participation was denied due to the fact that not all the conditions of the agreement between Pfizer and the NHS were public, and Pfizer still had ongoing negotiations regarding Tafamidis in other countries.

List of Interviewees, relevance and contribution to the case analysis:

1. **Ministry of Health – Dr. Manuel Teixeira** – Health Secretary of State – Was personally involved in the negotiation of the Tafamidis case at the time of the reimbursement. Working closely with Infarmed to analyse alternatives and solutions. Was also responsible for proposing the vertical financing model that was implemented to support drug's acquisition by the hospitals.
2. **INFARMED – Prof. Jorge Torgal** – Former president of INFARMED – Was the president of INFARMED at the time of the negotiation with Pfizer, regarding Tafamidis reimbursement. Presented its view on the deal and its outcome.
3. **CHPorto – Dr. Solari Alegro** – President of Centro Hospitalar do Porto (CHP), the main hospital unit regarding TTR-FAP treatment in Portugal. Was personally involved in the negotiations that occurred between the patient association and the MoH. Presented its view on the financing model implemented and its impact on the hospital side.
4. **CHPorto – Dr. Teresa Coelho** – Member of Hospital Santo Antonio, CHPorto Board, and director of the Centre for TTR-FAP treatment at the same hospital. Teresa Coelho developed for the main clinical trials performed with Tafamidis in Portugal. CHP's TTR-FAP Centre is the major of the 2 units in the country responsible for treating TTR-FAP patients. The interview focused on the diagnosis and treatment alternatives of TTR-FAP before and after Tafamidis introduction in Portugal.
5. **Patient association – Enf. Carlos Figueiras** – President of the major patients association in Portugal regarding TTR-PAF, Associação Portuguesa de Paramiloidose (APP). Carlos Figueiras was personally involved in the developments and the process regarding the market entry of Tafamidis in Portugal.
6. **APIFARMA – Dr. Heitor Costa** – Executive director of APIFARMA, Portuguese pharmaceutical industry association. Presented the point of view of the industry namely in terms of the concerns regarding patient's access to therapeutic innovation.
7. **Expresso – Dra. Vera Arreigoso** – Professional journalist working in the major weekly newspaper in Portugal, Expresso. Vera Arreigoso is dedicated to covering all health themes and provided a valuable view on the impact and responsibility of the media in the outcome of pharmaceutical innovation deals.

3. Theoretical foundations

3.1. Drug's market entry

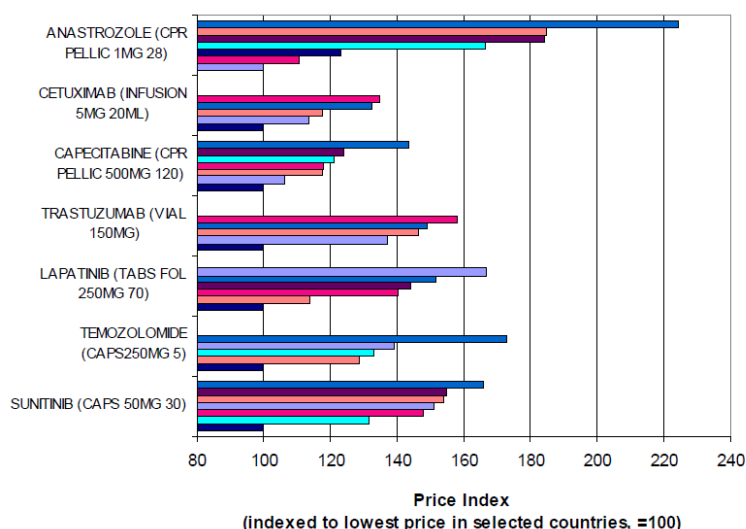
To analyse the process regarding Tafamidis market entry in Portugal it is relevant to have a deeper understanding on what are the procedures and requirements for a pharmaceutical product to obtain market authorization (MA) approval in Europe and in particular in Portugal. Only after obtaining that approval the product can be commercialized either in ambulatory or hospital market, according to the type of use and procedure performed. At this level it is especially relevant to analyse the specific conditions under which an orphan drug can obtain the MA, since those apply directly to the product under scope. On a second level it is relevant to understand what are the requirements for a product to obtain reimbursement, as this is a crucial condition for a successful product launch, namely in the hospital market, where Tafamidis is used. Without reimbursement a product is not available in the public hospital market as there is no authorization for its acquisition by public entities. Products that are commercialized in the ambulatory market without reimbursement can be acquired, but its cost must be supported directly by patients or their insurance/ private subsystems.

Barros and Nunes⁴⁵ consider a third level regarding market entry. Besides the MA and the reimbursement, the company has to want to commercialize the drug in the country. And this factor has been starting to be more relevant recently. According to Dr. Heitor Costa, *with the generalized reduction in prices in the pharmaceutical market, the introduction of a product in a country may not be interesting and that impacts on the access that the population has to therapeutic innovation*. One of the main factors that contribute to this situation is the international reference pricing system or external reference pricing. Reference pricing is used by several EU countries, including Portugal⁴⁶. This systems consists on creating a basket of countries where the product is already commercialized and defining the maximum price of a product as the average of the prices on the reference countries. In the figure 3.1 below it is possible to analyse the differences of prices for the same product that exist between different countries.

⁴⁵ Barros e Nunes, "10 Years of drug policy in Portugal", 2011

⁴⁶ Vogler S., "PPRI - Pharmaceutical pricing and reimbursement information", 2008

Figure 3.1 – Prices of selected cancer medicines across Europe, 2009



Marketing authorization

The process regarding the introduction of new drugs in the market has several steps to assure that it proves its value both in clinical and economic terms. The marketing authorization procedure is usually performed under a centralized procedure that is submitted and analysed at the European Medicines Agency (EMA) in the Committee for Medicinal Products for Human use. Under this procedure EMA analyses the clinical trials evidences provided by the submitting pharmaceutical company in what relates to the drug's efficacy, safety and quality. If approved centrally the MA is automatically extendable and applicable to Portugal. Locally, INFARMED only performs an administrative validation of the requirement, according to the applicable legislation⁴⁷. There are other types of procedures used to request MA in Europe, but are less used. One of the other options is a decentralized procedure, where the product is submitted to a country and then, if approved in that specific country, its approval can be generalized to other EU member states. Another alternative is to request local authorizations that only apply for a specific country.

Even without MA, some products may be used and commercialized under specific circumstances. In these situations hospitals must submit a request to INFARMED to acquire and use the product under an exceptional authorization procedure. This is only applicable in the following circumstances⁴⁸:

- Products without MA in Portugal but that have a well-defined evidences of clinical benefit (usually products that used to be sold in Portugal but were withdrawn by pharmaceutical companies)

⁴⁷ INFARMED, deliberation 1028/2009 (ambulatory) and Deliberation 1772/2006 (hospital)

⁴⁸ INFARMED, deliberation 1546/2015

- Products without MA in Portugal but that have preliminary evidence clinical benefits (usually innovative products without final MA approval from EMA)
- Product with a MA but that is not yet reimbursed.

Actually, in 2011 and early 2012, when there was clinical trials evidence but no MA, Tafamidis could fall under the second type of exceptional authorization mentioned above. But, according to Dr. Solari Alegro the use of these procedures *“is not good for the hospital, as the cost of the products will impact the hospital budget directly, without any additional sources of revenue”*, whereas if the product is already authorized and there is a central financing, there is a specific additional budget allocated.

Reimbursement

The reimbursement process is made locally by the marketing authorization holder in each country. The procedures required for reimbursement vary from country to country, as the product will be paid/reimbursed by each country. For a product to obtain reimbursement in Portugal it has to prove its therapeutic value added and its economic value. According to Carlos Ribeiro therapeutic value added means that *“a product has to prove its superiority (efficacy, safety, convenience) over the best available alternative in the market, or has to fill a gap in the market where there is no available alternative”*⁴⁹. In this last scenario the product only has to prove that it has a favourable benefit-risk ratio.

The therapeutic value added assessment is performed in Portugal by INFARMED. It consists in the compilation, analysis and evaluation of the results shown in the clinical trials performed with the drug, regarding efficacy and safety. This assessment has in consideration the indication in which the product is approved and the applicable clinical guidelines (national and international).

The economic value has to be proved using one of the following methodologies⁵⁰ that have the objective of maximizing the level of benefits with the least amount of resources available:

- Cost effectiveness – Benefits of different interventions are measured using a single outcome (e.g. life-years gained, deaths avoided, and increase in time to progression). Alternatives are then compared in terms of the Incremental cost of effectiveness ratio (ICER)
- Cost utility – Benefits are expressed as quality-adjusted life-years (QALYs)
- Cost benefit – Benefits are expressed in monetary terms
- Cost minimization – If benefits between alternatives are equal than cost should be compared

In what related to the decision to authorize reimbursement it varies according to the type of drug.

Ambulatory drugs have always been authorised by the MoH⁵¹, whereas Hospital drugs' reimbursement

⁴⁹ Ribeiro, C., “Health technology evaluation – Therapeutic value added, *revista Portuguesa de clinica geral*”, 2008

⁵⁰ Drummond M, Pereira J., Pinto, C., “ Methodological guidelines for drug’s health economics”, 1998

⁵¹ Law Decree 48A /2010

was decided by the INFARMED⁵². The procedure regarding Hospital drug's approval recently changed with the introduction of SINATS, centralizing all approvals within Ministry's responsibility⁵³.

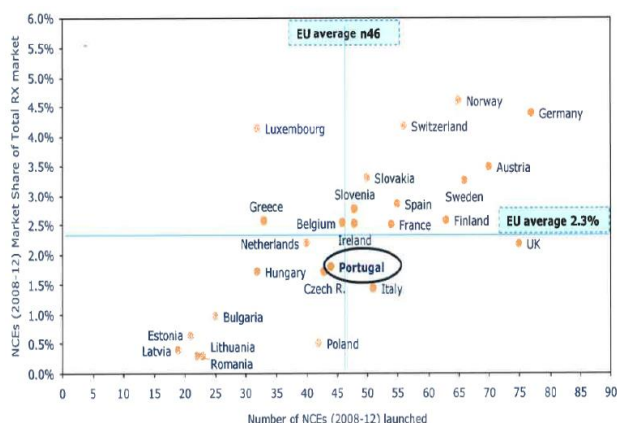
After approval in terms of reimbursement the hospital product has a last barrier to enter the market. The product has to be analysed by the National Pharmaceutical & Therapeutic Committee (CNFT) that will analyse if the product should enter the National list of approved hospital pharmaceutical drugs (*Formulario Nacional do Medicamento*).

3.2. Drug's access

Regarding the access to innovation, countries have different policies, profiles and results, but all share the common goal of providing best care for their citizens. Pharmaceutical innovation is a priority in EU countries. One of the main examples of this priority is the Innovative Medicines Initiative "*Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients*"⁵⁴.

Figure 3.2 compares the innovation profile of different countries, analysing the number of new molecular entities (NME) launched in the market and the market share obtained by these products, in order to measure the penetration and acceptance of these products in each country.

Figure 3.2 – Country Innovation profile (NMEs launched vs. market share achieved)⁵⁵



Analysing the results above it is possible to conclude that Portugal is above average in terms of the NME launched, but is lagging in terms of its adoption, meaning that besides market entry procedures there are other barriers to the access to these products, factors such as the delay in the reimbursement procedure,

⁵² Law Decree 195/2006

⁵³ Law Decree 97/2015 - SINATS

⁵⁴ <http://www.imi.europa.eu/>

⁵⁵ EFPIA (<http://www.efpia.eu/topics/industry-economy/access-to-medicines> - accessed September 2015)

and policies in place in hospitals that reduce the adoption of high cost drugs due to the impact that these have in their budget.

According to INFARMED, one of the main objectives of the pharmaceutical drug policy is “to assure access to drugs” but also to “assure the sustainability of the system, introducing criteria of rationality and efficiency in the management of hospital and ambulatory drugs”⁵⁶. The fact that INFARMED introduces these two statements in the objectives of the pharmaceutical drug policy shows a deep concern from public entities to ensure, on one hand, that there is actually access to innovative drugs, that will tend to optimize the health condition of the population, but at the same time the cost of those products must be reasonable not to put at risk the overall costs of the system.

According to a study performed by APIFARMA, that analysed the reimbursement requests from 2007-2011, there are difficulties in the access of innovative drugs or drugs with new indications in the Portuguese market⁵⁷. There are different factors that affect the entry of innovative drugs, but the main one relates to the high price of these new drugs. Different authors point to the fact that the current system of prices has to be reviewed, because countries can't cope with the high prices that are charged by the innovative products⁵⁸. The pharmaceutical industry has its products protected by a patent period to cover the high investment made in R&D, allowing the industry to sell their products in a monopoly market during that period, so there is a need to assure that prices are adjusted to that situation. The price of Tafamidis was definitely one of the main issues during the negotiation process, mentioned by all the study interviewees.

Another relevant point in what relates to access to the market in the administrative burden regarding the reimbursement procedure, and the time that it takes for analysis and decision regarding a reimbursement request. According to the study presented by APIFARMA the average duration for analysing a request was 331 days, increase to 634 in what relates to hospital drugs and even higher for areas like oncology (743 days) or orphan drugs (718 days)⁵⁹.

⁵⁶ INFARMED, “Drug policy goals” –

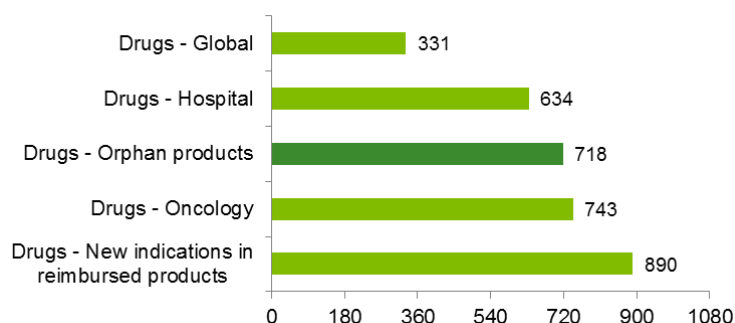
(http://www.infarmed.pt/portal/page/portal/INFARMED/PERGUNTAS_FREQUENTES/MEDICAMENTOS_USO_HUMANO/MUH_POLITICA_MEDICAMENTO - accessed Aug 2015)

⁵⁷ Felix, J., EXIGO – “Pharmaceutical drugs public financing in Portugal 2007-2011”

⁵⁸ Lamata F., Gálvez R., Barros P., Caro J., “Acceso a los nuevos medicamentos: El ejemplo de la Hepatitis C”, 2015

⁵⁹ Felix, J., EXIGO – “Pharmaceutical drugs public financing in Portugal 2007-2011”

Figure 3.3 – Reimbursement evaluation – time to decision in Portugal (median, days)⁶⁰



The fact that a reimbursement decision regarding an orphan drug takes approximately 2 years to decide actually increases the barriers to entry, going against the policy of EU, that wants to reduce the barriers in orphan drugs, as explained in detail in the next subchapter.

3.3. Orphan drugs

A disease is considered rare if its prevalence is lower than 5/10.000 people⁶¹. In Europe there are over 15 Million people with rare diseases, 600.000 in Portugal. In Portugal these diseases are addressed by the rare diseases program from 2008 that defines as its main objectives to⁶²:

- *“Improve the national healthcare responses to the unsatisfied needs of patients and their families;*
- *Improve quality and equity of care provided to rare disease patients.”*

Orphan drugs, like Tafamidis, are medicinal products that are *“intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition”*⁶³ in rare diseases. These products benefit from specific programs because, as they are applicable to a short population, there would not be an investment in them from pharmaceutical and biotech companies as they were not expected to generate high returns. The main incentives decided by EMA are the following⁶⁴:

- Access to centralized authorization procedure (single application for all EU countries)
- 10 years of market exclusivity in the rare disease indication (additional 2 years if product is extended to paediatric use)
- Additional incentives and research grants for SME companies

⁶⁰ Felix, J., EXIGO – “Pharmaceutical drugs public financing in Portugal 2007-2011”

⁶¹ Regulation (Ec) No 141/2000 Of The European Parliament And Of The Council, 1999

⁶² *Direção Geral de Saúde* – “Rare diseases national plan” 2008

⁶³ Regulation (Ec) No 141/2000 Of The European Parliament And Of The Council, 1999

⁶⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000393.jsp - accessed Aug 2015

- Fee reductions in administrative applications

This policy of incentives has been paying off, as pharmaceutical companies invested heavily in this niche markets due to its attractiveness. But the investment made and the innovative drugs that are coming to the market are pressuring the health authorities because the prices per patient have been increasing. According to a recent WHO study, new orphan drugs were seen as one of the major challenges as the *“average annual acquisition cost ranges from US\$ 200.000 - \$ 500.000 per patient per year. Actually the price of these medicines has been so high that some of these drugs have become “blockbusters” with sales over US\$ 1 billion per year in sales”*.⁶⁵ As the volume of patients is low the main growth drivers in this segment are price and the fact that as they are chronic diseases people will take the medication for a long period of time, in some cases, like Tafamidis, till the end of their lives.

In order to tackle the reimbursement process that in each country, EU developed a transparent value framework (TVF) assessment matrix to support the evaluation of orphan drugs, when there is little evidence. According to Dr. Heitor Costa this methodology *“is currently being implemented in Portugal to support the reimbursement process”*. The objective is to assure equity on the decisions applied throughout Europe.

Figure 3.4 – The transparent value framework matrix to access the value of orphan drugs⁶⁶

Criterion	Low degree	Medium degree	High degree
Alternatives available	Yes	Yes	No
Unmet need	New medicine does not address unmet need	Major unmet need still exists	No alternatives exist except supportive care and major unmet need exists
(Relative) effectiveness, degree of net benefit relative to alternatives including no treatment	Incremental	Major	Curative
Response rate	<30%	30–60%	>60%
Degree of certainty	Promising but not well documented	Plausible	Unequivocal

⁶⁵ WHO, “Access to new medicines in Europe”, 2015

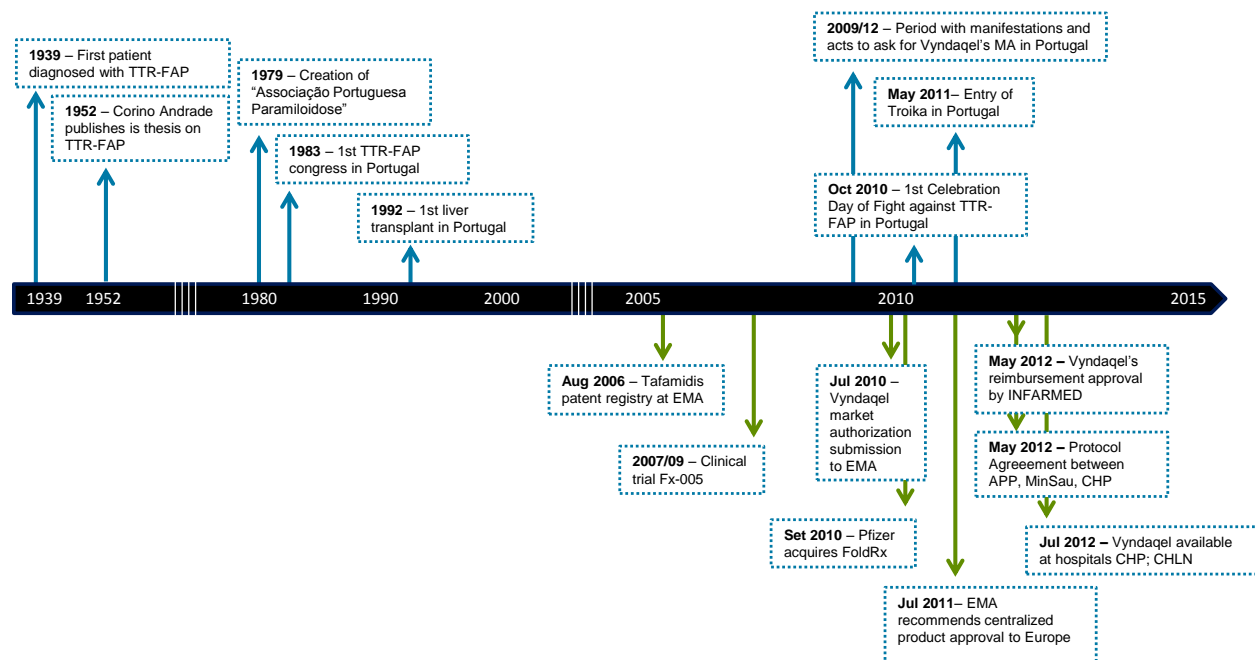
⁶⁶ EC – MoCA-OMP – “Key Conclusions and recommendations”, 2012

(http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process_on_corporate_responsibility/platform_access/index_en.htm - accessed Sep 2015)

4. Case analysis - The tafamidis deal

4.1. Introduction & timeline

In order to understand the case it is relevant to analyse in detail the main dates and events regarding Tafamidis and its introduction in the Portuguese market. Below is presented a chronogram with the main relevant events. All the information required to build this chronogram is available in the student's case.



1939 & 1952 – The disease was first discovered in 1939 by Corino de Andrade, a Portugal physician that studied and documented it in its thesis, published some years later in 1952⁶⁷. These dates are relevant to understand that the disease had its origin in Portugal, and is quite known by the Portuguese population. The fact that it was a "Portuguese" disease was one of the main factors that was relevant for Pfizer in the selection of the market and for the MoH and INFARMED, when analysing its reimbursement.

1979 & 1983 – The creation of "Associação Portuguesa de Paramiloidose", one of the oldest patient associations in Portugal shows the relevance of this disease in the Portuguese context. It is also relevant to understand that this specific association that had a major impact in the negotiations held regarding Tafamidis, was established in the market for more than 30 years prior to Tafamidis appearance. The association was responsible for the organization of the 1st TTR-FAP congress in Portugal, back in 1983.

⁶⁷ Vieira, B. "Thesis TTR-PAF Type I – A current vision of an old health issue", 2008

1992 – This date signals the first liver transplant in Portugal. Before 1992 there were no alternative treatments for this highly incapacitating neurodegenerative disease. The 1st world transplant related to TTR-FAP had been performed in 1991 in Sweden, just 1 year before, showing that Portugal was on the edge of innovation in the management and treatment of this disease.

2006 – In August of this year FoldRx submitted the patent registry regarding Tafamidis. This date is relevant to the calculation of patent protection, as the period of patent protection starts.

2007/09 – During this period FoldRx conducted the main phase III double blind clinical trial Fx-005, that compared Tafamidis against placebo in an 18 months study with 91 patients, showing that the proportion of patients who experienced no deterioration in neurological impairment (no progression of neurodegeneration) was higher in the Vyndaqel population. 60% against 38% in placebo population.

2009/12 – During this period, and after the announcement of Fx-005 clinical trial results the pressure from patient's and patient associations increased since many of the patients on the study were Portuguese and were already receiving treatment and feeling the positive results of Tafamidis. It were made several actions and initiatives to demand the product's reimbursement.

2010 – This is a crucial year for the product, since it is the year where FoldRx is acquired by Pfizer, and is the year of the submission of the marketing authorization request to EMA, the relevant authorities in Europe.

2011 – In July the product obtains approval from EMA, one year after the request. The approval confirmed the product's value in clinical terms, increasing the pressure over national authorities for its introduction and reimbursement in the market. In Portugal this is a transition year in political terms, as the previous socialist government is replaced by a new democrat regimen, and it is also the year when Portugal requests Troika intervention to finance the economy. The acceptance of Troika's terms and policies would impact severely in the pharmaceutical market.

2012 – Between 2011 and 2012 there are several developments in terms of the deal between Pfizer and the MoH in order to obtain product's reimbursement that occurs in May. Previous to the deal it is also celebrated an agreement between the MoH, Centro Hospitalar do Porto and the patients association, APP, stating that the product would be reimbursed and available for the patients. In July the product starts to be used in the 2 hospitals that would concentrate the treatment of TTR-FAP patients: CHP and Centro Hospitalar Lisboa Norte (CHLN).

4.2. Questions

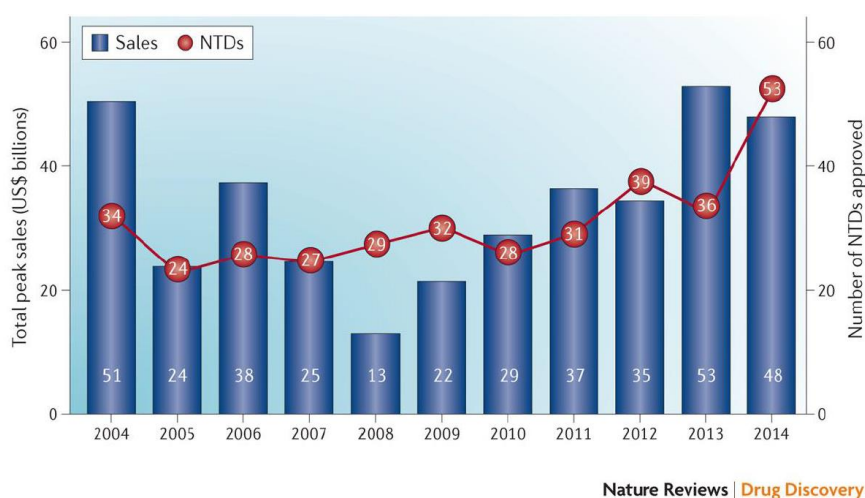
i. Why was the introduction of Vyndaqel in the Portuguese market so relevant for Pfizer?

The context in Portugal was adverse to the introduction of new molecular entities. There was a high pressure on costs imposed externally by troika that entered in 2011 and internally by the entry of a new and stricter policy from the MoH that imposed several cuts in healthcare in order to control overall healthcare expense.

Analysing annex 1 of the student's case it is possible to conclude that, at that time, Portugal had a higher level of health expenditure as a share of GDP (10.2%) than the average of OECD countries (9.3%), and even higher than other Southern European countries like Spain (9.3%), Italy (9.2%) or even Greece that was also under the intervention of Troika (9.1%). This factor is mainly due a low GDP since when analysing the healthcare expenditure per capita Portugal is below average. The same situation occurred when analysing the proportion of medical goods cost over the current health expenditure (annex 2) or the pharmaceutical expenditure as a share of GDP (annex 3). Portugal has 23% of costs related to medical goods whereas OECD countries' average is 20% and Spain only has 21%. These differences between Portugal and other countries in terms of overall indicators showed that there was "space" to impact and reduce costs in the pharmaceutical market. The entry of Troika and its policies impacted heavily in this demand, the market started reducing its value from 2010 onwards, mainly in the ambulatory market, but also on the hospital side (annex 4). From 2008 till 2012 Portugal had the 2nd highest fall in the European pharmaceutical market size reducing an aggregate of more than 20% (annex 5), only surpassed by Greece with a cut of 26%, way below EU average that accounted a positive growth around 4%.

Analysing the graphic below it is possible to identify a fall in the overall revenues of pharma companies starting in 2004 and having its lowest point in 2008. Regarding the approval of NTDs (New therapeutic drugs) the number of new products was fairly constant. In 2010 pharmaceutical companies were still feeling a shortage in the introduction of innovation in their portfolios, picking up in the years after that. There was a higher level of pressure felt in the market around the introduction of new products to create successful launches. So every launch was relevant and every market counted.

Figure 4.1 – Approval of NTD and sales generated⁶⁸



Pharmaceutical specialty care units often dedicate to orphan drugs like Tafamidis because these products have government incentives to its production due to the limited number of patients, usually have high prices and have patent protection for a period of 10 years after MA.

Financially, Pfizer was under pressure in the Specialty Care Unit that was responsible for the introduction and management of innovative specialty products in the hospital market. Analysing the results shown in annex 7 related to Pfizer International, there was a reduction of 7% from 2011 to 2012 in total revenue in the SC&O Unit. Additionally, and analysing the Pfizer stock market price it had its lowest peaks in 2009 and 2010. Pfizer invested a lump sum of around \$400M in the acquisition of FoldRx in 2010, where the main company asset was Tafamidis, the innovative drug that would bring a new hope to the treatment of TTR-FAP, a highly incapacitating rare disease. Its launch was critical to assure the return on the investment made, and Portugal was a key market as it was historically “the market where it all begun” and had a high prevalence.

The pain point in the reimbursement process was the product price, due to the international reference pricing system. The definition of price in Portugal was relevant as it had a large market but most of all this price would serve as reference to other major countries, like Brazil, where there were also relevant populations of TTR-FAP patients. Depending on the price set there would be a direct impact on product's profitability the entry in the Portuguese market was critical for Pfizer.

Orphan drugs are also relevant from a social point of a view for companies like Pfizer. By investing in niche populations companies show to the market their investment in the health in general, and that they provide care even to small populations that otherwise wouldn't have access to pharmaceutical innovation.

⁶⁸ Mullard A., “Nature Reviews Drug Discovery - 2014 FDA Drugs approvals”, 2015

ii. What should NHS take into consideration when analysing the reimbursement decision?

NHS has in its core values that it has to provide healthcare to all citizens. And the population always wants access to more and more innovative care, with pharmaceutical innovation at the top. As the population pays taxes that flow into the NHS they always ask for more, without taking into consideration the costs that are indirectly paid by them. This effect is known as moral hazard because there isn't a direct link between the payer and the beneficiary, what creates a distortion in the market. So the NHS has to make choices by the population because they need to manage the national health budget assuring an adequate and efficient use of its funds. Choices like, should the Ministry of Health allocate funds to the creation of a new hospital, like the *Hospital Oriental de Lisboa* that is foreseen to replace the CHLC, allowing for better care in newer and more modern facilities, or should they direct that same investment to other health priorities, like prevention, enlarging the access to vaccines or increasing the number of screening tests performed in areas like diabetes or oncology that affect millions of peoples in Portugal? Where does Tafamidis, an orphan drug for a small group of patients, fall in the list of priorities?

When comparing drugs there are specific methodologies to compare alternatives from an economic point of view. That is the role of pharmacoeconomic and incremental cost-effectiveness ratios (ICER) is the main ratio used to compare such alternatives. The procedures of “*avaliação previa*”⁶⁹ support the hospital reimbursement decision in Portugal, but there are no formal set criteria that state when a drug should or shouldn't be reimbursed. According to Prof. Jorge Torgal “*there should be an intense analysis and debate regarding this theme as this is critical to support decisions*”. In other countries, like England there are criteria and boundaries set that support comparability between decisions. NICE sets that a drug should be reimbursed if the cost per QALY is between £20,000–30,000⁷⁰. On the table below it is possible to analyse that different thresholds have been discussed, but the fact remains that in Portugal there is no formal decision about this subject.

⁶⁹ Law Decree 97/2015 - SINATS

⁷⁰ McCabe C., “The NICE cost-effectiveness threshold: what it is and what that means”, 2008

Figure 4.2 – Cost effectiveness thresholds⁷¹

Cost-Effectiveness Thresholds Referenced by Authors of U.S.-Based Cost-Utility Analyses, 1990–2012. ⁷²			
Threshold	1990–1999 Analyses (N=207)	2000–2009 Analyses (N=851) <i>percent</i>	2010–2012 Analyses (N=444)
\$50,000 per QALY	19.3	36.6	36.9
\$100,000 per QALY	6.3	7.8	16.9
Both \$50,000 and \$100,000 per QALY	3.9	19.9	23.7
Other	18.4	10.6	7.4
No threshold referenced	51.9	25.1	15.3

* Data are from the Tufts Medical Center Cost-Effectiveness Analysis Registry (www.cearegistry.org). QALY denotes quality-adjusted life-year.

In order to analyse the impact to the NHS, and to the society the company also has to present budget impact estimates, that take into consideration on one hand the increase of costs, namely the price of the product for the treatment of a population, and on the other hand the costs that are saved due to the entry of this innovative product, namely in terms of future complications (direct costs) and in the reduction of productivity / payment of anticipated pensions (indirect costs).

According to Eurico Castro Alves, current INFARMED president *“the acceptable value of an innovative drug is the one that corresponds to the drug’s added value assuring that access can be given to all that benefit from it, without putting the NHS in jeopardy (...) therefore the negotiation phase of the reimbursement is fundamental to assure access to all citizens that benefit from the innovative drug at an affordable price for the NHS”*⁷².

Tafamidis pricing decision

The pharmaceutical market is regulated in Portugal and there is an international reference pricing system that sets the entry price according to the average of the prices of the drugs in the countries that compose the reference basket. This is the maximum price that a product can be sold in Portugal. After this, in non-centralized procedures, each hospital may obtain discounts that make the product more affordable. But in the Tafamidis case the reference pricing system didn’t apply directly. Because this can only be applied if the product is commercialized in the reference countries and there is already a price set. Even without reference prices, Tafamidis was already being commercialized in some EU countries under exceptional authorization procedures. That was the case of France, where, according to Enf. Carlos Figueiras *“the cost of a patient per year was around 135.000€”*. In England, according to a budget impact analysis to

⁷¹ Neumann, P. “Updating Cost-Effectiveness — The Curious Resilience of the \$50,000-per-QALY Threshold”, 2014

⁷² Newspaper “Diário de Notícias”, May 2015

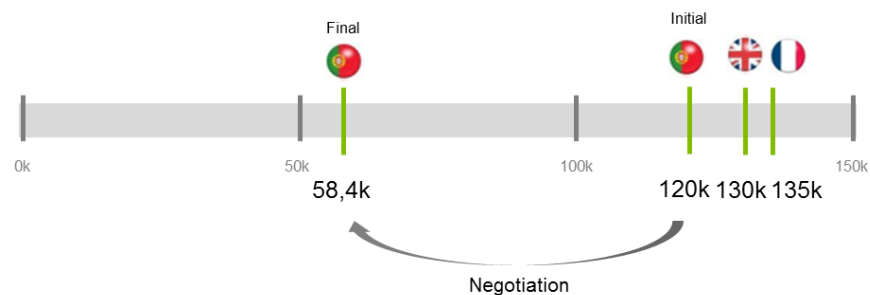
(http://www.dn.pt/portugal/interior/inovacao_ministerio_negoceia_precos_de_remedios_oncologicos_4577215.html - accessed Aug 2015)

evaluate the impact of the acquisition of Tafamidis for a period of 5 years, the yearly estimated cost per patient was around at 130.000€⁷³.

From the NHS point of view there were 2 main factors to take into consideration when analysing Tafamidis price. On one hand what were the future costs saved with this new drug, direct costs associated with TTR-FAP complications that could be avoided like hospitalizations, transportation or the cost of transplantation. Indirect costs associated with loss of productivity from patients and their families should also be taken into consideration. On the other hand was the clinical benefit of the product. Even though there weren't solid long term evidence of the benefits of the product, clinical trials showed statistically relevant differences in disease progression during the clinical trial period.

In Portugal, there is no official information regarding the initial price proposed by Pfizer, but according to the information available the negotiation started around 120.000€⁷⁴ and the final approved value was around 58.400€⁷⁵. Not publicizing the acquisition cost of a drug has been becoming a regular request from the industry. INFARMED reimbursement reports may not include the final price of the agreement, as it was the case of Tafamidis. If a price is not public it can't be used as a reference price for other countries, increasing Pfizer's negotiation power in those countries.

Figure 4.3 – Tafamidis price comparison between countries



Analysing the information provided in annex 9 it is possible to determine the actual costs incurred by the NHS with Tafamidis reimbursement. Around 4,1M€ in first year (2012), 14,4M€ in the second year and 18,2M€ in 2014. An estimate of around 310 patients was under treatment in 2014.

⁷³ Faria, R. "TTR-FAP Evidence Review Group assessment of manufacturer submission", 2012

⁷⁴ GAPPAP, 2011

⁷⁵ Nº 13/2014/DPS/ACSS

iii. What were the positions and arguments of each party (NHS vs. Pfizer) in the deal regarding Vyndaqel's reimbursement?

In any negotiation there are two sides that have different interests, different objectives and different constraints. In this case the sell side was Pfizer that wanted to introduce the product in the market and obtain reimbursement for it, and the buy side was the Ministry of Health that represented the hospitals that would acquire the drug for the patients. The achievement of a deal results from a comprehensive process that involves both sides. Each presents its own point of view on the deal under consideration. The pharmaceutical market, and all the negotiations involving the reimbursement of medicines go beyond the typical market rules because human life or at least the quality of life is at stake. According to Dr. Heitor Costa, APIFARMA's representative, *"the price of an innovative drug is related to its value. The value of a pharmaceutical product can't be seen as a price to cover production + R&D costs. The market doesn't work like this"*. Nonetheless the price assumes a vital role in the negotiation. Borges, A.⁷⁶ presents his view regarding the high cost of a new drug, relating it to 3 main factors:

- *"High costs in R&D, namely the investment on clinical trials to generate evidence of the efficacy and safety of the drug;*
- *Time value of money, since the process of introducing a product in the market ranges from 12 to 15 years, reducing the time of commercialization under patent protection;*
- *High number of failures in the development of new drugs, meaning that the product that gets MA will have to compensate the company from those costs."*

Arguments like these were certainly used by Pfizer to support the initial price presented to the authorities. And the price of the drug is the pain point of any negotiation. From a theoretical point of view in a negotiation each side, has a reservation price. This is the value till where each party is willing to go during the negotiation. So, during the negotiation each side presents arguments that defend their position in order to explore the surplus of the other side. On the seller side Pfizer wanted to maximize the price, while the MoH wanted the opposite, to minimize the price to make it affordable to the NHS, and available to all the patients that would need it.

The main argument presented by Pfizer was related to the clinical value of the product, and to the innovation that it brought to a disease, where there was no real alternative apart from liver transplantation that had several risks. The clinical trials performed by Pfizer supported that the proportion of patients who experienced no deterioration in neurological impairment (no progression of neurodegeneration) was higher in the Vyndaqel population. 60% against 38% in placebo population. This highly incapacitating disease finally had an alternative in its treatment process. A lifesaving alternative. Portugal, the country where it all begun had to deliver this treatment to its patients and their families, because this didn't just

⁷⁶ Borges, A. *"Inovação em saúde – Presentation under Innovation in health class – FEUP"*, 2012

affected the patients, their families were always involved. Additionally Vyndaqel was already being used by some Portuguese patients that were enrolled in the clinical trial, and the drug was available in other countries in Europe like France or the United Kingdom, there was no reason why the product should not be reimbursed in Portugal.

On the government side the main arguments were regarding the lack of solid information to support the reimbursement and the severe economic conditions that Portugal was facing in 2011, under the intervention of Troika. INFARMED's reimbursement report states that *"(...) in conclusion the drug has therapeutic value added despite its modest efficacy, fills a therapeutic gap and reduced disease evolution in at least 20% of the patients"*⁷⁷. According to Prof. Jorge Torgal the clinical trials that were presented only had a limited time frame and therefore there were no specific results that could support a long term evaluation. No one could claim that the product was in fact lifesaving, as there was no long term results to support it. Additionally there was only one main trial to support the decision with few patients. Why should the NHS support the high cost of this drug if there were no real evidences? Analysing the extreme economic conditions of Portugal didn't favour an agreement as the NHS could not support to treat all the patients in need if the price of the drug was so high. In order to lower the price to more affordable terms the NHS had on its side the fact that Portugal was a relevant market for this product, with a high number of patients. The volume was one of the main factors to support the decrease of the price, as the agreement wouldn't treat some specific patients under an exceptional authorization procedure, it would assure access to all patients that complied with the set clinical criteria.

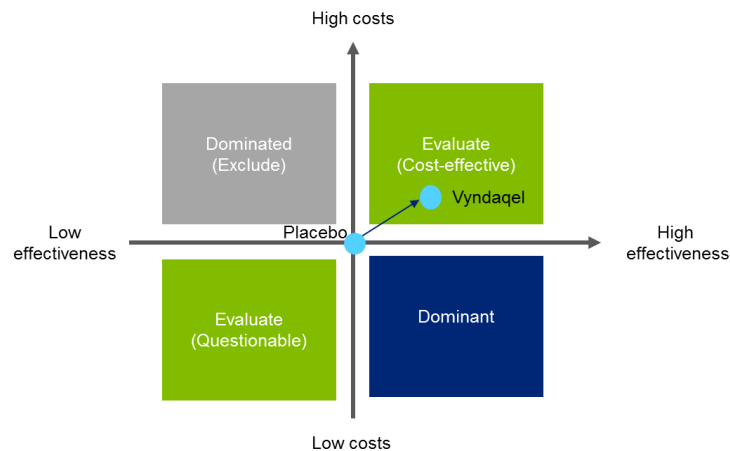
As mentioned before the final agreement supported a price around 58,4k€ per patient, less than 50% of the initial 120k€ that were supposedly presented as the initial price. The final INFARMED report that supported Vyndaqel's reimbursement stated that *"the maximum acquisition price of Vyndaqel for NHS hospitals resulted from a pharmacoeconomic evaluation and a negotiation procedure with Pfizer taking into consideration the severe exceptional conditions supported by Portugal as well as the high prevalence of TTR-FAP in Portugal."*⁷⁸

In summary, from an economic point of view Vyndaqel proved to be more effective, even though more costly when compared to placebo, as shown in the figure below. So there was a need to include other factors in the decision to reimburse the drug.

⁷⁷ INFARMED, "Tafamidis hospital use - Reimbursement report"; 2012

⁷⁸ INFARMED, "Tafamidis hospital use - Reimbursement report"; 2012

Figure 4.4 – Pharmacoeconomic evaluation of Tafamidis ⁷⁹



iv. **What was the role of the patient's associations and the media in the process?
Was it good for the deal?**

As mentioned in the case there are 2 main patient associations related to TTR-FAP in Portugal. “Associação Portuguesa de Paramiloidose” (APP), active since 1979 and “Grupo de Apoio à paramiloidose”, created in 2007. Both associations developed several actions after the first public positive results of the clinical trials with Tafamidis in 2009. Till this date its activity was mostly dedicated to supporting the patients and their families and to increasing public awareness and information level regarding the disease. But in 2009 patients started to pressure the associations for a more active role in the disease management. According to Enf. Carlos Figueiras *“APP met with all the parties that were represented in the House of Parliament”*, alerting to the relevance of the disease, its impact on patients, their families, the NHS and the country as a whole. The main focus was to increase awareness that there was a treatment for this highly incapacitating disease and that it was not available for the Portuguese patients. In 2011 it was actually submitted a public petition (annex 11) requesting Tafamidis as a first line in the treatment for TTR-FAP patients.

The MoH was contacted daily by the patient associations to know if there were new developments regarding the reimbursement decision. There were several actions on the streets, in front of the MoH, in front of the main reference hospital, Santo Antonio in Oporto, and these actions were covered and publicized by the media. According to Dr. Vera Arreigoso *“these type of actions are always covered by the media due to its relevance to the public”*. According other international journalist *“The role of the media has always been to be the voice of the people, to ask the questions they cannot of the people they*

⁷⁹ Adapted from Drummond, “Methods for the economic evaluation of healthcare programs”, 1997

*cannot get to*⁸⁰. So the media plays a major role in the process as it has the effect to amplify the actions taken by the parties, namely the patients.

Hospital administrators, pharmaceutical association representatives and journalist interviewed in this case all agreed that actions taken by patients and patient associations on the streets, in public events, and the coverage provided by the media to these type of manifestations, where these stakeholders show their discontent with the fact that there is a drug that might be able to “save” them but is not yet available in the market, increases the priority given to the matter by the MoH. Prof. Jorge Torgal stated that with the patients on the streets and the pressure of the media “*the drug had to be made available*”.

According to the legislation in place in 2012 the decision of reimbursement regarding hospital products relied in INFARMED’s authority, whereas ambulatory products reimbursement decision was approved and signed by the MoH. But in cases with high economic impact and high media coverage there is also a political side that has to be considered. That is one of the reasons why the MoH becomes involved in these type of decisions.

The relationship between the pharmaceutical industry, the medical community and patient associations has always been under high scrutiny from regulatory entities, as there are points of interests from the parts in what relates to bringing a drug to the market. Historically the pharmaceutical industry has always supported patient associations because, on one hand they are their final client, and even though they can’t publicize directly to the patient, they can support them on specific actions, and on the other hand they want to create awareness about the disease and its treatment options available in the market. Positioning has a key stakeholder that contributes to the management of a disease not just as a vendor, but as a real partner that is interested in the wellbeing of people is key for pharmaceutical companies. For instance that is one of the reasons why Pfizer supports initiatives like orphanet⁸¹, related to the management of rare diseases, where TTR-FAP is included.

According to Dr. Heitor Costa “*companies that are part of APIFARMA have always been obliged by their internal policy to disclose the grants and other payments made to HCP and HCO. By doing this the industry fosters a transparency policy in the market*”. For example it is possible to analyse Pfizer’s website to consult the amounts paid to healthcare organizations related to TTR-FAP initiatives. By analysing annex 10, it is also possible to conclude that the majority of the financial support provided by Pfizer happened in the year of the product reimbursement and the year after that (2012 and 2013). The disclosure of these type of financial support to healthcare practitioners (HCP) and healthcare

⁸⁰ Willey J., “Is the media weaning itself off drugs? Why access to cancer drugs keeps returning as a media issue” (<http://www.hanovercomms.com/2015/01/is-the-media-weaning-itself-off-drugs-why-access-to-cancer-drugs-keeps-returning-as-a-media-issue/#sthash.DvZagsmL.dpuf> – accessed September 2015)

⁸¹ <http://www.orpha.net/national/PT-PT/index/parcerias/>

organizations (HCO) was actually recently legislated⁸², obliging the pharmaceutical companies to disclosure and report to INFARMED the financial support provided.

In summary, the fact that there were actions on the streets asking for Tafamidis reimbursement, and the fact that the media gave coverage to those actions had two contradictory effects. On one hand it created a buzz around the disease and the treatment, bringing it up to the front pages of newspapers and making the MoH get involved directly in the deal that otherwise would have been solved by INFARMED. This fact made the process go faster. But on the other hand the fact that there is pressure on the deal tends to worsen the conditions obtained in the negotiation in terms of price, resulting in a worse deal for the NHS and indirectly for the patients. In fact MoH and INFARMED were representing the patients and their best interests but the pressure made on the streets reduced their time to negotiate, what may have resulted in worst deal conditions for NHS.

v. Which method should the NHS use to acquire Vyndaqel?

Financing schemes of innovative therapeutic drugs are one of the main topics in healthcare. With, on one hand, the increased pressure on the healthcare budget, that results in the need to reduce or at least contain costs, and on the other hand the society pressure for access to innovative products there is the need to find alternative models to the traditional price-volume finance schemes.

According to WHO there are 2 main types of agreements that can be celebrated between payers and the pharmaceutical industry, regarding drug financing⁸³:

- Financial agreements (does not consider drug outcome)
 - Price-volume agreements – There is an expenditure threshold, after which a rebate is applied on the volume exceeding that threshold;
 - Discount/rebates – Price is set and paid in full to the vendor, and then there is a refund of the agreed rebate. This solution may also be applied to a portfolio of products;
 - Capping schemes - Implementation of a cap regarding total treatment cost, where after that cost if there are additional treatments are supported by the vendor. Capping may be set by population, number of treatments or total cost.
- Outcome-based agreements (considers drug outcome in real-life: effectiveness)
 - Risk sharing (Payment by result/performance) – Reimbursements are linked to a set outcome, if the outcome is not reached the government may not pay or pay partially;

⁸² Law Decree 20/2013 and Law Decree 128/2013

⁸³ WHO, "Access to new medicines in Europe", 2015

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- Success sharing – This agreement is relevant when there is a high probability of success and the government wants to minimize the risk of having a high cost in the future for a long term;
- Coverage with evidence development – Reimbursement is conditional to the collection of further real-world evidence to support the outcomes. When data is presented the reimbursement is reviewed according to the cost-utility/effectiveness data provided.

Regarding Vyndaqel it was celebrated a financial agreement with cap. According to Dr. Teresa Coelho the initial agreement between Pfizer and the MoH/INFARMED defined that it should be included 280 patients (240 in CHP + 40 in CHLN) with a budget cap for its treatment at 30M€ for the first 2 years. Also according to Dr. Teresa Coelho, *outcome based agreements were not possible to use in a drug like Vyndaqel because it was quite difficult to define the outcome to measure.*

The second part relates to the way Vyndaqel should be acquired and how should the budget be allocated from the NHS to hospitals. In Portugal, hospitals celebrate an annual management agreement (*contrato programa*) with ACSS, the central administration health authority. The current model relies on a production base agreement with a component of risk sharing between the hospital and the NHS, in order to incentivize hospitals to reduce costs. If they produce more than 10% of what is contracted with the NHS, they won't be paid for that. Additionally there are specific programmes related to specific disease management (eg. HIV patients) where the hospital receives a comprehensive price to pay for the whole treatment costs associated to a patient.

Regarding Tafamidis it was settled a specific vertical line of financing for 2 specific hospitals (CHLP and CHP). According to the pharmaceutical industry one of the main advantages of vertical financing schemes is the fact that it allocates a budget specific to an end. In this way hospitals can't use this funding to their daily operational activities, meaning that there isn't an opportunity cost associated to these funds, as the money can't be used to any other end than the payment of Vyndaqel. The fact that the financing was centralized in 2 main hospitals was also relevant in order to assure equity in terms of the criteria applied to the selection of patients with access to the treatment and it also favoured the control of the expenditure due to the centralization in terms of budget allocation.

4.3. Future

With the decision to reimburse Vyndaqel patients started to have access to the drug, initializing its treatment according to the clinical guidelines defined. In order to continuously monitor the effects of the treatment with Vyndaqel it was initiated an observational study, THAOS (Transthyretin Amyloidosis Outcome Study)⁸⁴. This is one of the aspects that was required in the decision to reimburse the product, that there would be additional collection of evidence to support study results. Actually this type of licensing, that request for additional evidence is becoming a new alternative contracting model called adaptive licensing⁸⁵ / adaptive pathways⁸⁶ where, reimbursement is given for

Other alternatives for the treatment of TTR-FAP are in study like antisense approaches from ISIS or siRNA technologies from Alnylam, but so far Tafamidis remains the only approved alternative for TTR-FAP treatment.

⁸⁴ Coelho, T. "Long term effects of Tafamidis for the treatment of transthyretin familial amyloid polyneuropathy", 2013

⁸⁵ Eichler, H. "Adaptative licensing: taking the next step in the evolution of drug approval", 2012

⁸⁶ EMA "Pilot project on adaptive licensing", 2014